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Arteriosclerosis Cardiovascular Disease

Their Relation to Infectious Diseases

BY

WILLIAM OPHÜLS
Professor of Pathology

From the Division of Pathology
Stanford University Medical School

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ARTERIOSCLEROSIS CARDIOVASCULAR DISEASE THEIR RELATION TO INFECTIOUS DISEASES

WITH SIXTY-ONE CASE RECORDS

The problem of the origin and development of arteriosclerosis has been attacked by many investigators in a great many ways, but in spite of all efforts, an altogether satisfactory solution has not been found.*

THEORY OF AN INFLAMMATORY ORIGIN

Virchow's(1)† original conception that the process was of an inflammatory nature was comparatively simple and in spite of all objections, it is well not to lose sight of the fact that certain evidences of inflammation are present in the early lesions of non-specific arteriosclerosis both in the diseased intima and about the vasa vasorum in the adventitia. (Koester.) In fact, the accumulation of leucocytes, even of the polymorphonuclear neutrophilic type, is sometimes quite well marked in the early intimal lesions. It is also certainly true that, although the infectious and distinctly inflammatory lesions of syphilis are usually easily distinguished from the ordinary forms of arteriosclerosis, in the aorta as well as in the cerebral arteries, it must be acknowledged that this distinction becomes more difficult and sometimes nearly impossible in those cases in which the changes brought about by syphilis develop more gradually or where the actual infection has already subsided. Even at the present time therefore there are some investigators who adhere to Virchow's original idea. Aufrecht(2), e. g., states quite positively: "From a purely anatomical point of view I feel justified in looking upon the process in arteriosclerosis as an inflammation of the vasa vasorum which leads to trophic disturbances in media and intima." Klotz(3) also emphasizes the inflammatory changes that take place in the arterial walls in arteriosclerosis, and Sumikawa(4), who carefully examined 100 cases of arteriosclerosis of the aorta, comes to the conclusion that arteriosclerosis is a chronic productive inflammation.

THEORY OF A MECHANICAL ORIGIN

More recently it has become customary to look upon arteriosclerosis as a partly degenerative, partly reparative process, resulting from the wear and tear to which the arteries are exposed in the course of human life—from stresses of a more physical nature and from toxic lesions associated with various intoxications and infections. This reversal of opinion was brought about primarily by Thoma's famous work on the origin of the arteriosclerotic thickenings of the intima, as a result of which he came to the conclusion that these thickenings were caused by a local or general giving way of the arterial wall, and that their formation tended to reëstablish the normal shape and caliber of the lumen of the blood vessels. His fundamental conception of the process he has recently formulated in this way: "The growth of the transverse diameter, or of the circumference of the lumen of a blood vessel depends upon the rapidity of the blood stream. It begins, when the stream velocity of the layers of the blood flowing close to the vessel wall exceeds a certain threshold value which I shall designate as v, and within certain limits it is the more rapid the more the rapidity of the stream increases beyond the threshold value v. *On the other hand, a negative growth, a decrease in the circumference of a blood vessel, occurs when the velocity of the layers of blood flowing close to the vessel wall decreases below the threshold value v."* (Italics ours.) The latter is what, according to his views, happens in arteriosclerosis.

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* For a more extensive historical review see: Faber, "Dis Arteriosklerose." Jena. Gustav Fischer. 1912.

† Figures in parentheses refer to bibliography.

As attractive as such an almost mathematical formulation of a general law governing physiologic and pathologic growth processes in blood vessels might appear, it must not be overlooked that some of the premises from which Thoma has deduced his logical conclusions are far from incontrovertible; in other words, it is by no means proved that the intimal thickening must in all cases be preceded by a dilatation of the vessel wall, resulting in slowing the current at that point. In fact, personal experiments with Thoma's methods seemed to be distinctly unfavorable to his contention. Still Thoma's rather convincing presentation of his thesis has aroused a great deal of interest in the subject as a whole and has therefore been of great benefit. Jores(5), who has made a particularly intensive study of the role of the elastic tissue in arteriosclerosis, although opposed to Thoma's doctrines, has borrowed his idea of the importance of physical factors in the development of the disease. He believes that one can distinguish histologically between those chronic lesions of the arteries which are the result of what he terms endarteritis and those of true arteriosclerosis in which there is a hyperplastic development of the elastic tissue in the intima plus connective tissue growth and tendency to degeneration. He acknowledges, however, that this distinction is not always readily made. According to him, true arteriosclerosis is to a great extent the result of physical stress acting upon the arterial wall, and in this way his teachings harmonize well with the ideas of many clinicians who assume with Huchard that arteriosclerosis is more frequently the result of chronic hypertension in the arterial tree than its cause, as was believed formerly.

This same idea of the importance of mechanical factors is also very definitely expressed in Faber's excellent monograph on arteriosclerosis (l. c.), in which he states his first general conclusion as follows: "Arteriosclerosis is a disease of the blood vessels, which develops as a result of a disproportion between the strength of the vessel wall and the height of the blood pressure."

These views have been elaborated considerably by Aschoff(6). He looks upon the disease as the result of either diffuse or local wear and tear which through changes in tension necessitates the building in of new either elastic or fibrous structures.

Marchand(7) on the other hand emphasizes the degenerative character of the lesions and in order to give clear expression to this conception proposes to change the designation to *athero*sclerosis.

In America most careful anatomical investigations into the nature of arteriosclerosis have been made by Klotz, and his attitude seems to be that, while acknowledging the importance of physical strain, he is still of the opinion that there is in the process an inflammatory component which should not be overlooked.

EXPERIMENTS WITH ADRENALIN AND OTHER TOXIC SUBSTANCES

It was largely to test the mechanical theory of arteriosclerosis that Josué(8) undertook his well-known experiments with adrenalin and showed that, by intravenous injection of this blood-pressure-raising substance it is possible to produce in rabbits a disease of the aorta resembling arteriosclerosis and eventually leading to aneurismal dilatation. Much of the early hope, however, of a complete solution of the problem through these experiments has been dissipated by the recognition that the experimental disease, although similar to certain types of arteriosclerosis, cannot be identified with it and that it is not caused by the rise in blood pressure but by toxic action of the adrenalin. The same effect may be produced by various other poisons which do not raise the blood pressure.

CHOLESTEROL FEEDING EXPERIMENTS

Much interest has also been aroused by the experimental work inaugurated by Ignatovski(9) in an effort to ascertain the effect of certain diets upon the arteries, as a result of which it eventually developed that the feeding of rabbits with sufficient quantities of cholesterol or cholesterol-containing substances causes the development in the aorta and pulmonary arteries of these animals of patchy lesions filled with cholesterol fat which in every way exhibit a most remarkable resemblance to early atheromatous change in the human arteries. Here, again, it must be borne in mind that these results, so far, have been largely obtained in herbivorous animals whose metabolism is evidently not attuned to the prompt handling of large quantities of these materials, so that, besides in the normal reservoir in the adrenals, the cholesterol fats are deposited, not only in the intima of the blood vessels mentioned, but also in the parenchyma of various other organs like the spleen, kidneys and liver. There is some doubt, therefore, of the applicability of these experiments to human pathology, but, if they mean anything, they certainly suggest that the lipoids found in the atheromatous lesions are not necessarily the result of degenerative changes, but may be absorbed into the intima from without, and, if their presence here does not actually cause the disease, it may at least aggravate the pathological process. This latter possibility had already been suspected by pathologists, before the experimental evidence had been forthcoming. In discussing this question in his lecture on arteriosclerosis Aschoff[6] recalls Ribbert's(10) suggestion that the peculiar swelling of the intima in early arteriosclerosis might be due to imbibition with blood plasma from the blood circulating in the vessels and develops the idea that the lipoid material also might be carried in with the plasma.

It is unfortunate that the endothelial lining of the large blood vessels is lost so soon after death, so much so that it is practically impossible to obtain evidence of its condition during life. Otherwise one might be able to test the assumption that primary endothelial damage may be the cause of this imbibition with plasma, and of the entrance into the intima of lipoids and even some of the white blood cells, which we usually find there. The whole process would then constitute a real inflammation of a peculiar order, consisting first of injury to the endothelium, then of the entrance into the intima of plasma carrying along the lipoid substances and some few leucocytes. This idea is only a modification of some old views on the subject which had been generally abandoned.

CLINICAL VIEWS

Clinicians, naturally, have paid particular attention to the functional disturbances associated with arteriosclerosis. Several of these clinical problems are relatively simple, like that of the origin and the clinical effects of areas of arteriosclerotic softening in the brain; others are exceedingly complex like the question of the relation of arteriosclerosis to hypertension and its associated phenomena. In our country this latter symptom complex has lately been designated more or less aptly "cardiovascular disease." In this connection the fact cannot be over-emphasized that arteriosclerosis is a purely anatomical term and cardiovascular disease a purely clinical designation of a functionl state. They are not at all superimposable like original and image as is still loosely being assumed by so many.

To my mind one of the most important contributions which the clinicians have made to the subject has been the discovery that the rise in blood pressure frequently precedes the development of severe anatomical changes in the arteries. For this reason the certainly erroneous idea has gained wide acceptance, that the hypertension in itself is one of the causes of the development of the anatomical lesions. The mere fact that there are cases of "essential" hypertension, so called, which persist for many years without leading to arteriosclerosis, seems to negative this assumption. But however that may be, it cannot be too strongly insisted that all evidence seems to point to the fact that not only early in the disease, but often quite to the end, the rise in pressure is largely the result of functional disturbances in the arteries and not the result of a damming up of the blood by an irremovable physical obstacle. The French clinicians, Huchard and others, first placed the right emphasis on this fact, and we are also indebted to them to a great extent for their constant insistence that there is apparently some relation between certain general infections and arterial disease. I have been particularly interested in this latter question, and for this reason I wish to discuss our present knowledge on the subject somewhat more in detail.

RELATION OF INFECTIOUS DISEASES TO ARTERIOSCLEROSIS

There are various ways of approaching this problem; first by an anatomical investigation of the lesions in arteriosclerosis; second, by anatomical study of the immediate effects of infectious diseases on the arteries; third, by experimental research with bacteria and bacterial toxins; fourth, from a clinical point of view, by a careful scrutiny of the history of the patients, and by reëxamination of patients who had at one time suffered from certain severe infections which are suspected of causing lasting damage to the arteries.

All these methods have been employed, but so far without entirely conclusive results, but we may say, in general, that there is a strong suspicion expressed by many, both pathologists and clinicians, that severe infections or intoxications are perhaps more important in the development of chronic arterial disease than any other one factor.

The results of anatomical and histological research have already been discussed. Here everything seems to favor the theory of a mechanical or nutritional origin of the disease. It has been suggested, however, that infectious diseases may injure the arterial walls in such a way that they tend to earlier and more rapid decay, and that in this manner infection might be of importance in the development of arteriosclerosis.

As stated before, the relation of infectious diseases to arteriosclerosis first attracted the attention of clinical observers, but definite evidence as to their interrelation has been accumulating very gradually.

When in 1881 Hippolyte Martin(11) was studying the progressive obliterating types of endarteritis in the various organs of the body he was naturally most interested in the acute forms which occur in young individuals, and from his observations he already then concluded that this type of arterial disease was evidently caused by various acute infections, instancing particularly observations made in cases of diphtheria and typhoid fever. He thought that these changes resulted from the direct contact of the arterioles with the microörganisms which were present in the blood stream.

In 1893 Thérèse(12) wrote a very elaborate thesis on the inflammations of the arteries resulting from infectious diseases. He collected quite a series of cases of young individuals with early arterial lesions and tried to demonstrate that in all of them infectious diseases played an important role. The infections which appear most frequently in his histories are typhoid fever and smallpox. In order to test his theory he also made experimental investigations which will be mentioned later.

Similar researches conducted by Simnitzky(13) in 1903 brought out a history of infection in about two-thirds of the cases. According to his tables, the infectious diseases most important in this regard seem to be tuberculosis, typhoid fever, chronic sepsis, and chronic endocarditis.

The greatest interest was aroused by the very careful and painstaking anatomical work of Wiesel(14) in 1906. He made routine examinations, both gross and microscopical, of the aorta and many smaller arteries, in 300 cases of acute infections. The patients had been mostly children and young adults, and his investigations covered the following infectious diseases: diphtheria, scarlet fever, measles, varicella, pneumonia, influenza, septic diseases, and typhoid fever. The most severe lesions observed could be seen with the naked eye as yellowish, slightly sunken spots, but usually the changes were revealed by the microscope only. The pathological alterations were primarily located in the media and consisted in an initial serous infiltration followed by necrosis of the muscle and breaking up of the elastic tissue. The largest foci were about four-fifths of a millimeter in diameter. They apparently healed by scar formation. The lesions were probably of toxic origin and were seen most frequently in diphtheria and scarlet fever. Wiesel considers these changes as precursors of arteriosclerosis, and as such they have been commonly accepted because this assumption fitted in very well with the general conception that lesions of the muscular and elastic elements of the arterial wall were essential in the development of the disease.

In the same year Wiesel(15) made a separate report on the coronary arteries and stated that in them the disease almost constantly extended to the intima, causing visible slightly elevated yellow patches from the size of a pin's head to that of a lentil, so that in the coronaries there is an early resemblance to true arteriosclerosis.

These observations of Wiesel were immediately confirmed by Wiesner(16); later by Scharpff(17), who, however, did not find the changes as regularly nor as extensively.

In our own country Frothingham(18) in 1911, as a result of similar studies, came to the conclusion that "in certain of the acute infectious diseases diffuse arterial lesions exist which may be the result of toxic action. . . . Some of these lesions will undoubtedly leave on healing a permanent sclerosis of the arterial system." He found these changes most consistently in diphtheria, pneumonia, tuberculosis, typhoid fever, and glanders.

McMeans(19), a pupil of Klotz's, believes that he finds the early stages of a process which later might develop into arteriosclerosis in the lesions observed in the arteries in more chronic forms of meningitis. These lesions in the meningeal arteries are often very striking and definitely of an inflammatory character. They apparently commence in the intima of the affected blood vessels.

By his very careful investigations Faber (l. c.) satisfied himself that the earliest signs of arteriosclerosis consist in loss of elasticity in the media and beginning calcification in this region. He believes that this condition may be brought about quite rapidly by acute infectious diseases and is frequently associated with chronic infections such as tuberculosis, syphilis, chronic intestinal stasis, etc. He is convinced, therefore, that chronic infections, more especially tuberculosis, play a very important role in the production of arteriosclerosis. He also thinks that alcoholism is important, because arteries weakened by its abuse are more frequently affected by infectious diseases. His final conclusion is: "The larger the number of diseases suffered, the more marked probably the arteriosclerosis of that individual."

After the experiments of Ignatovski and others had called attention to the importance of cholesterol-containing substances, Zinserling(20) pointed out that deposits of anisotrophic lipoids may be found in the intima of the aorta in young individuals in various infections, especially in typhoid fever. These lesions he looks upon as early stages of arteriosclerosis and interprets them as a result of the possible influence of infectious diseases upon the metabolism of cholesterol.

EXPERIMENTAL WORK WITH BACTERIA AND BACTERIAL TOXINS

It has already been mentioned that the French clinicians have been particularly interested in the relation of infectious diseases to arteriosclerosis; it is therefore not surprising that most of the experimental work along this line has been done in that country.

Gilbert and Lion(21) were early pioneers in this field. In 1889 they described lesions in the aorta of rabbits following intravenous injection of typhoid bacilli and of organisms obtained from malignant endocarditis. In some of these experiments the aorta had first been traumatized by means of an aseptic needle.

Crocq(22), who made similar experiments, became very strongly impressed with the necessity for previous vascular injury. He claimed that the bacillus isolated by Gilbert and Lion from malignant endocarditis was the only organism which attacked the intact arterial wall, and he believed that in man also some lesion or nutritive disturbance of the arteries must precede the action of the bacteria or their toxins in producing arteriosclerosis.

Thérèse(12), whose anatomical and clinical studies have been spoken of, inoculated rabbits intravenously with colon bacilli and streptococci and as a result observed areas of round-celled infiltration about the blood vessels which he regarded as precursors of arteriosclerotic changes. He obtained similar results in guinea pigs inoculated with diphtheria bacilli of low virulence and in one rabbit after intraperitoneal injection of a filtered streptococcus culture.

The destructive effect of diphtheria toxin upon the blood vessels of guinea pigs and rabbits has later been described by Mollard and Regaud(23) in 1897.

In Italy Pernice(24), in 1895, obtained results very much like those of Thérèse by means of injections of cultures of staphylococcus aureus, of anthrax bacillus, and of diphtheria bacillus.

The most exhaustive studies of all are those by Boinet and Romary(25), published in 1897. Contrary to the usual experience, they found streptococci in what they considered early arteriosclerosis lesions of the aorta in a man dead of erysipelas and in another patient who died of rheumatic pericarditis. These findings, so far as I have been able to ascertain, have never been duplicated by others. They then performed numerous experiments in rabbits by means of intravascular or subcutaneous injections of various bacteria, including the bacillus typhosus, bacillus coli, streptococcus, staphylococcus, bacillus anthracis, and bacillus tuberculosis, usually following traumatism of the aorta. They obtained quite a number of positive results, and in one animal, where there was a plaque of 3 by 2 millimeters in diameter, they even found the streptococci in the proliferating intima. They succeeded quite as well with bacterial toxins, of which they employed tetanus and diphtheria toxin, tuberculin, the toxins of streptococcus and those of the spirillum of Asiatic cholera. They also claimed positive results following experimental administration of lead, uric acid, phloridzin and to some extent of mercury. They also reported arteriosclerotic lesions in the aorta of a horse that had been used in the production of diphtheria antitoxin.

Following these early experiments there is quite an interval of time until this line of work was resumed by Klotz (1906), Saltykow (1908), Manouélian (1913), and Bailey (1917).

Klotz(26), after intravenous injection of typhoid bacilli and streptococci, found warty thickenings in the first part of the pulmonary artery and in the ascending limb of the aorta. The microscope revealed degenerative and regenerative processes in the intima and of the inner layer of the media.

Saltykow(27) observed very typical atheromatous lesions in the aorta of rabbits after repeated intravenous inoculations of staphylococci of low virulence, and Manouélian(28), experimenting with suspensions of killed staphylococci or filtrates of staphylococcus cultures in rabbits and monkeys, frequently obtained lesions in the media of the aorta which evidently closely resembled those produced by adrenalin.

Klotz(26) already had noticed that it was possible by injections of diphtheria toxin to produce lesions in the aorta of rabbits which closely resembled those caused by adrenalin injections. This was confirmed by Bailey(29), working in our laboratory, who observed very extensive medial degeneration, sometimes followed by calcification, not only in the aorta but also in the larger arterial branches after intravenous injections of large doses of diphtheria toxin in these animals.

On the other hand we never have been able to obtain any characteristic results by intravenous injection of various microörganisms except in a very few instances in which a slight endarteritis of some of the small organ-arteries was seen after repeated intravenous injections of living streptococcus cultures in rabbits.

In reviewing the results of these experiments, I believe one is justified in stating that, although suggestive, they are hardly conclusive enough to permit of direct application to human pathology. The changes are usually quite limited and more or less inconstant. A condition resembling general arteriosclerosis in man, or even well advanced atheroma of the aorta, has not been produced.

There remains to be considered a large body of evidence connecting certain special infections with chronic arterial disease. Some of it revolves around what the French have described as acute arteritis. Such cases of acute bacterial infection of the arteries have a definite bearing upon our problem, because it is to be presumed that, if certain infections at times cause acute arterial diseases of a serious character, the same infections may more frequently involve the arteries in a milder fashion, laying the foundation for future mischief.

SEPTIC INFECTIONS

As a rule the arterial wall seems to be very resistant to septic infection, and phlegmonous infiltration or abscess formation has been described only in the wall of the aorta, and even there very rarely.

Andral(30) in 1827 reported a case of multiple abscess formation between the intima and media of the aorta, and Virchow(31) in 1847 one of an abscess in the wall of the aorta which had been mistaken for atheroma. Eppinger(32) in 1868 made an observation similar to the latter one.

The report of Stumpf(33) in 1913 of a diffuse phlegmon of the aorta probably due to streptococcus infection, in a man of 54 suffering from tabes and cystitis, seems to be unique in literature.

Infectious ulcers at the base of the aorta are, of course, quite common in septic endocarditis and the aortic wall is often sufficiently deeply destroyed to cause the formation of aneurisms. Ulcers not more or less immediately connected with ulcerative lesions on the valves, on the other hand, are again quite rare. Turner(34) (1886) described one in a woman of 48, dead of sepsis, and the most interesting observation of this kind seems to be that of Vanzetti(35), in which there were multiple circumscribed ulcerations and dilatations with yellow borders of purulent infiltration. The base of the ulcers was formed by granulation tissue in which there were few remnants of media. In the lesions pneumococci (probably diplo-streptococci) were demonstrated.

Osler's(36) case was somewhat similar but associated with ulcerative endocarditis.

Oliver and Woodhead(37) reported a large perforated ulcer in the base of the aorta without endocarditis which they believed to be due to infection with anthrax bacilli. The identification of the latter, however, is very incomplete.

Occasionally bacteria are found in old atheromatous ulcers, but their presence is evidently due to secondary invasion.

In a few instances vegetations like those occurring on the aortic valves have been found in the aorta. Observations of this kind have been placed on record by Barbacci(38), Buhl(39), Heydloff(40), and Nauwerk and Eyrich(41). The most typical case of this kind, recorded by Bouley (42), showed these deposits near the last intercostal arteries and a somewhat similar plaque further up near the arch.

Infectious Aneurisms

Infectious aneurisms of the arteries are usually the result of septic embolism, as was first clearly recognized by Eppinger(43). Such an embolus lodges in an artery, infects the wall, partly destroys it by causing ulceration, and the result is an acute aneurism. This type of arterial infection may occur in any artery, but it has been observed most commonly in the cerebral arteries of individuals suffering from septic endocarditis, where it is frequently followed by haemorrhage into the brain. Most of the apoplexies in early life are due to this cause. More difficult to explain are the infectious aneurisms of the aorta or of the large arteries, often associated with septic endocarditis, but occurring also independently of it, in the production of which such gross embolism cannot very well play any role. Just as in later years syphilis is the usual cause of aneurisms, so septic infection causes by far the greater number of them in childhood and early adolescence.

Quite a few clinical observations of this kind have been recorded, but the number of those which were examined anatomically is not so very large. In the cases of Teile(44), McCrae(45), Gambaroff(46), and Neuber(47), the aneurisms were situated so close to the diseased aortic valves that there is a possibility of contact infection from floating vegetations, but both McCrae(45) and Gambaroff(46) received the impression that the infection of the aortic wall had originated in the adventitia as a result of septic embolism of the vasa vasorum. This was also the opinion of Klotz(48) in his case in which the aneurism was somewhat further removed from the valves. No valvular disease was present in the observations of Jordan (49) and Koritschoner(50), but there was a general streptococcal sepsis starting in one case from a severe phlegmon of the hand and in the other from an old otitis media.

In the abdominal aorta these aneurisms occur either at the upper end or below, near the bifurcation. Of the former type we observed one in our laboratory in a young girl. The aneurism was situated in the region of the renal arteries, one of which was partly obstructed by it. Many streptococci were found in the thrombotic masses contained in the aneurism. There was no endocarditis and the primary focus was not discovered. The child had suffered from chronic sepsis and nephritis.

Those near the bifurcation appear to be more common, cases of this kind having been described by Alexejeff(51), Simmonds(52), and Baginsky(53). In the last case there was no endocarditis.

The question whether in these cases the infection of the aortic wall takes place from the inside or whether through the vasa vasorum by way of the adventitia is not entirely settled, but there is no reason why both forms of invasion might not be possible and actually realized in different cases.

An example of an infectious aneurism of a small artery, apparently not due to gross embolism, is found in Ruge's(54) observation of an acute infectious aneurism of the left coronary artery without endocarditis following acute osteomyelitis of the femur.

In smaller arteries, of course, the uncertainty always arises whether an infectious embolus had not been present which eventually had dropped into the aneurism and had been lost in this way, but in the cases of Parker(55) and Lindbom(56), in which the aneurisms were in the iliac arteries, this seems hardly probable. Parker(55) in 1884 already concluded: "The condition which leads to plastic inflammation in one part of the arterial system, may produce local changes in the other parts, which permits the development of aneurism without the immediate intervention of an embolus."

What interests us particularly is, that in more chronic cases of this kind a chronic inflammatory process may occur in the vessel wall which causes much thickening and scarring and may lead to more chronic forms of aneurism like those in syphilitic disease of the aorta; in fact, in some of these cases a syphilitic origin has been suspected, to my mind erroneously. The cases of Smyth(57), Sanné(58), Aitken(59), Huchard and Bergouignen(60), Libman(61), Wilson and Marcy(62), and of Humphry(63) belong to this group. Sanné(58) states that the inner surface of the arch was covered with "atheromatous" deposits; Aitken(59) describes two bulging "atheromatous" plaques in the arch, which he believes eventually would have developed into aneurism. In Libman's(61) case the lesions were of such a chronic nature that he doubts their mycotic origin. In Wilson and Marcy's(62) observation the aorta was much thickened and showed "atheromatous" patches. Humphrey(63) made a careful histological examination of the wall of the pulmonary artery in which the lesions were situated in his case and found in the tunica media at intervals numerous areas of proliferating cells, polymorphonuclear leucocytes and lymphocytes. In places the muscle had disappeared entirely. No bacteria were found in sections. All these observations were made in children and young adults from 4 to 22 years of age, so that syphilitic aoritis and ordinary atheroma may be fairly readily excluded. Huchard and Bergouignen(60) come to the conclusion that infections of the aortic wall may produce either ulceration and acute aneurism, or they may aggravate chronic processes, or they themselves may sometimes produce chronic lesions terminating in aneurism.

Acute Arteritis

This brings us to the consideration of what has been described by French clinicians as acute arteritis, a condition sometimes observed in septic infections and in rheumatic fever. There is considerable dispute about the question as to whether in these diseases the manifestations described cannot better be explained as resulting from embolism, as suggested by Blot(64), a pupil of Lépine's, but this will hardly cover those observations in which the diseased arteries did not become obstructed.

The series of observations of this character starts with a most remarkable description of Tufnell(65) in 1853 of a patient suffering from endocarditis, who first showed painfulness and excessive pulsation of the tibial arteries, later similar symptoms of the brachial artery, "then leaving this spot, local arterial throbbing setting in consecutively in different portions of the circulatory system." A more characteristic case of multiple acute arteritis could hardly be imagined, but unfortunately there are very few such striking instances recorded in literature. De Fajole(66) in 1866 described a fairly conclusive case in which consecutively both carotid arteries became involved. Neither Tufnell nor de Fajole states positively that the arteries remained patent, but Barié(67) followed the whole course of events carefully in a gardener, 24 years of age, who on the fifteenth day of an acute rheumatic fever developed an acute inflammation of the brachial artery. The artery at first was dilated and painful, later contracted, and in the end apparently returned to a normal condition.

Conti's(68) patient showed an arteritis of the left carotid and Roche and Burnaud(69) observed pains in the arteries of the arms and legs with transitory obstruction in a man of 31 years who was suffering from an old rheumatic endocarditis.

Cases of acute aortitis of the abdominal aorta under similar circumstances have been described by Thoinot(70), Teissier(71), and Conti(68). Teissier(71) found in one of his cases at autopsy a large rose-colored gelatinous plaque in the abdominal aorta, but the interpretation of these gelatinous plaques as characteristic of acute aortitis is more than doubtful.

From this review it is evident that the number of fairly typical cases of acute arteritis in sepsis and rheumatism is so small, and there has been such a lack of opportunity for careful anatomical examination, that one is hardly justified in making positive assertions, like those which one finds in Queuille's(72) thesis, where it is definitely stated that rheumatism produces sometimes acute arteritis, that this condition may heal, but may also be followed by aneurismal dilatation, or by total obliteration, or may eventually become chronic and produce arteriosclerosis. The latter assertion is also made by Barié(73) in his more general article in 1913.

Roche and Burnaud(69) distinguished two types of the disease, one in which the arteries remain open and the other in which they become closed. In the latter case gangrene or infarcts may threaten or actually result, as in the cases of Meade(74), Leyden(75), Barraud(76), and Eichhorst(77). In Eichhorst's patient, who had an oral mitral endocarditis, the thromboses were multiple in the splenic, left renal, superior mesenteric, both common iliac, both femoral and left common carotid arteries extending into the left external and internal carotids and into the left superior thyroid arteries. There were also thrombi in the abdominal aorta, the right pulmonary artery and the vena cava. In microscopic section the intima was normal, but there was a round-celled infiltration about the vasa vasorum. No bacteria could be demonstrated, still Eichhorst feels convinced that the thromboses were due to an inflammation of the vessel wall caused by bacteria or their toxins.

We are particularly well informed in regard to the effect of the rheumatic infections on the coronaries, because these changes have been the subject of very exhaustive anatomical investigation. Romberg(78) first emphasized the frequency of sclerosis of the muscular branches of the coronary arteries in chronic endocarditis, and suggested that this sclerosis probably commenced with an inflammatory infiltration in the adventitia of the affected arteries. He cautiously adds: "It may be conceived that the sclerosis of the coronary arteries in valvular disease of young individuals develops partly on an inflammatory basis." The same suspicion is even more strongly expressed by Rabé(79) in 1902. Cowan(80) in 1903, on the basis of the study of an acute and of a more chronic case, emphasizes the tendency to acute endarteritis in the smaller branches. Coombs(81) (in 1907) noted both endarteritis and periarteritis, and Geipel(82) in the same year described a case with very severe lesions in the small and medium-sized branches resembling those observed in the periarteritis nodosa with beginning aneurismal dilatation of a small branch. Gallaverdin(83) found fibrous thickening of the walls of blood vessels in old myocardial scars. More recently (1912) Klotz(84) made a very careful study of the aorta and of the coronaries in fifteen cases of rheumatism in different stages and comes to the following conclusions: "The arteries react to the irritant in a true inflammation and this reaction is to be observed in the adventitia and outer portion of the media. In the acute stages the inflammatory exudate is of non-suppurative variety in which the lymphoid cell is most prominent. The inflammation occurs particularly in the neighborhood of the smaller arteries, while the medium-sized vessels are little affected. On the other hand, the larger arteries, which are supplied in their outer coats by nutrient vessels, are damaged by the inflammatory process, which travels along the vasa vasorum." "In the aorta the destruction of tissue is particularly noted in the loss of muscle and elastic elements." "The intima does not appear to be primarily affected. In the early stages a slight superficial fatty change is sometimes noted, while later in the chronic stages the intima proliferates, giving rise to nodular endarteritis." "Thus the aorta in chronic rheumatism is disturbed by a patchy fibrosis better spoken of as chronic productive mesaortitis."

According to this description the chronic disease of the aorta appears to bear a more close resemblance to chronic syphilitic aortitis, than to ordinary arteriosclerosis, or might possibly be said to form a connecting link between them, but there seems to be considerable evidence that in the coronaries, apart from the destructive type so well described by Geipel,[82] there are also found proliferative lesions which may terminate in endarteritis.

Clinical Relation of Rheumatism to Arteriosclerosis

It is said that Bouillaud(85) (1840) was the first to suggest the clinical relation of rheumatism to arteriosclerosis; in two of his cases of rheumatism he suspected the disease had affected the arteries in one and the aorta in another. In 1864 Lemaire(85a), a pupil of Gunéneau de Mussy, states positively that in the great majority of cases the arterial lesions are of an "arthritic" nature. Fernet(86) in 1865 concludes that acute rheumatic arthritis often prepares the way for an ulterior arterial degeneration. Lécorché(87) in 1869 considers it self-evident that rheumatism affects at the same time the endocardium and the intima of the arteries.

In his general discussion of the causes of arteriosclerosis Guéneau de Mussy(88) (1872) states that among 140 cases of arterial lesions, he found 86 which had presented rheumatic manifestations, and two years later(89) he made the following more specific statement: "So, summing up, acute articular rheumatism preceded the arterial lesion in 34 cases, chronic rheumatism in 5 and other forms of gouty or rheumatic diathesis in 27," and remarks that probably the part played by arthritism and rheumatism is more extensive than his figures appear to indicate.

Hanot(90), in reporting a case of acute articular rheumatism in a boy of 18 with endocarditis of the aortic and mitral valves, in whom he found what he considered early atheromatous lesions in the aorta, states that he has observed several similar cases, and comes to the conclusion that arteriosclerosis, which according to him usually is of infectious origin, may sometimes follow an acute rheumatic arteritis. Bureau(91) (1895), although convinced of the importance of rheumatism in the development of general arteriosclerosis, seems to think that atheroma is due to trophic disturbances, but may be aggravated by intercurrent attacks of rheumatism.

It is of particular interest, in view of the preceding statements, to hear the judgment of Poynton and Paine(92), to whom we owe so much of our modern knowledge in regard to the rheumatic infections. They are extremely guarded in their conclusions. "The rheumatic infection, although it may produce an arteritis, does not appear to damage the arteries to any great extent in the young, and in the older subjects it is difficult to decide, when there is extensive arterial change, what part, if any, the actual rheumatism has taken." They also state, "It is quite possible, though incapable of proof, that some mild degree of infection of the vessels may occur without being of any clinical importance, but among results possibly a tendency to spasm should be added"; and "The perivascular fibrosis that occurs in numerous lesions of rheumatism may possibly, when extensive, produce some injurious result upon the circulation by curtailing the vascular supply and raising the blood pressure, but it is a result that it is difficult to appreciate."

PNEUMONIA

Acute infections of the arteries seem to occur occasionally in pneumonia. Poynton(93) describes a case of acute aortitis associated with fatal pneumonia in which he demonstrated the pneumococci in the subintimal tissue. What may have been an infectious aneurism, according to Clutton and Dudgeon(94), occurred in the femoral artery of a man of 78; at least pneumococci were found in the sac of the aneurism, but the authors suggest that the bacteria might very well have settled in a pre-existing aneurism. Several cases of arterial thrombosis in pneumonia, possibly following acute arteritis, may be found in literature, such as those of Blagden(95), Berthier(96), M'Gregor(97), and Brouardel and Giroux (98). Blagden(95) particularly emphasizes the great tenderness over the entire course of the diseased femoral artery in his case.

So far as the effect of the pneumococci on the small arteries is concerned, Wadsworth(99) in his study of the endocardial lesions developing during pneumococcus infections in horses gives an interesting picture of a marked endarteritis in a small artery. (Plate IX, fig. 13.) He does not refer to this matter in the text.

No evidence has been brought forward to show that pneumonia may ever leave permanent defects in the arteries.

SCARLET FEVER

Any arterial lesion that may occur in scarlet fever most likely would be the result of the associated septic infection. Very little is known in regard to them except for a few observations of arterial thrombosis following scarlet fever reported by Schott(100), Pearson and Littlewood (101), and Eichhorst(102).

There is also a somewhat doubtful case of acute arteritis of the internal carotid followed by aneurismal dilatation and ending in recovery described by Lyot and Petit(103).

Wiesel(14) quite commonly observed medial necrosis in the arteries of the cases of scarlet fever which he studied.

SMALLPOX

In smallpox also one naturally would attribute considerable importance to the associated septic infections, but in spite of the older reports of vascular, especially aortic, lesions in this disease by Portal(104) and Brouardel(105) nothing definite has been heard since.

GONORRHOEA

The observations of arterial disease following gonorrhoea are equally rare. There are few cases of acute gonorrhoeal infection of the aorta described by His(106), Aubry(107), and Guillain and Rendu(108). We observed a case rather similar to the one reported by Guillain and Rendu (108) in which there was a deeply ulcerated patch in the arch of the aorta 2½ centimeters above the aortic valves covered with thrombi. Gonococci were demonstrated in the lesions. There was also present an old ulcerative endocarditis.

DIPHTHERIA

In spite of the above-mentioned toxic lesions produced in the arteries of rabbits by diphtheria toxin, very little seems to be on record regarding any effect of this disease upon the arteries of man. Little fatty spots are frequently found at autopsy in the aorta and sometimes in other large arteries. The early degenerative lesions described by Wiesel(14) occurred in 40 out of 100 cases of diphtheria. Huguenin(109) in 1890 described a marked endarteritis in diphtheritic myocarditis, but his observations were not confirmed by Rabot and Philippe(110), who could find evidence of periarteritis only.

TYPHOID FEVER

Typhoid fever is the only disease in which there can be no question of the occurrence of an acute arteritis, and much of the French opinion in regard to arteritis has been built up about this condition.

What first attracted attention to arterial disease in typhoid were cases of gangrene, usually of the lower extremities, due to arterial thrombosis. In his thesis Ferraud(111) gives an excellent historical review of the early knowledge on this subject: how Bourgeois d'Étampes(112) in 1857 first definitely recognized the relation of typhoid fever to the gangrene and of his discussions in regard to this matter with the Société des Hôpitaux in Paris, and how Bourguet d'Aix a few years later performed the first conclusive autopsy. Patry de Sainte-Maure(113) in 1863 already recognized that an inflammation of the arterial wall was the cause of the thrombosis and very graphically described the appearance of the diseased arteries which, according to him, are injected, thickened, friable, have lost their elasticity and are filled with soft thrombus.

Graber(114) described the first observations of this sort in Germany and refers back to an old case of Rockitansky in 1849. Burlureaux(115) and Lereboullet(116) also published some early cases, and in 1878 Potain (117) observed two cases in which there was intense pain "in the arteries of the left leg with cessation of pulsation which, however, later returned. He argued from this that there must be cases of typhoid arteritis without thrombosis and distinguishes between what he calls obliterating and parietal arteritis. A considerable number of similar observations were then collected by Barié(118) and Deschamp(119).

Barié(118) apparently made his first microscopic examination of the wall of one of the diseased arteries and found necrosis and round-celled infiltration.

The later reports by Guyot(120), Gaston(121), Vulpian(122), Drewitt(123), Duchesne(124), Loring(125), Thayer(126), and Chauffard(127), did not add much to our knowledge, but in 1895 de Quervain (128) found typhoid bacilli in pure culture in an abscess in the popliteal space in connection with a typhoid arteritis, and ten years later Rist and Ribadeau-Dumas(129) demonstrated the typhoid bacilli in the wall of the diseased artery. This latter finding we have been able to confirm in a case observed in our laboratory in which there was present a typhoid arteritis of the arteria dorsalis penis with thrombosis followed by gangrene of the penis and part of the scrotum.

From all this it is quite evident that typhoid bacilli not at all rarely invade the wall of the larger arteries, cause serious disease of the arterial wall and may cause thrombosis as a consequence.

The effect of typhoid fever on the smaller arteries was first studied by Hayem(130) (1869) on a specimen of diseased rectus muscle with large haemorrhages. In sections from this specimen he found a marked endarteritis in some of the small arteries. He also reports later (131) that he has discovered similar processes in small branches of the coronaries in cases of sudden death in typhoid. Landouzy and Siredey(132) examined the heart of a patient who had died of cardiac weakness two years after having had typhoid fever. They found old and more recent myocarditis and obliterating endarteritis. Rattone(133) in 1887 published a very elaborate paper on this subject. He even demonstrated the typhoid bacilli in the inflamed arterial wall in a case of acute endarteritis of the branches of the coronary artery of a girl of 20, who died suddenly of myocarditis following typhoid. The presence of endarteritis in such cases was later confirmed by Hobbs(134) and Romberg(135), although the latter seems to doubt the frequency of this occurrence.

Naturally the question arises, what are the late effects upon the arteries of a disease which attacks them so acutely at times? An attempt to answer this question has been made by Thayer(136) who reëxamined a considerable number of patients who had had typhoid fever some time before. He found that the average systolic blood pressure was appreciably higher than in normals; in many instances it exceeded what is usually regarded as normal; the radial arteries were easily palpable in a large proportion of the cases (three times as many as in controls); the average size of the heart was larger; in eight cases discharged with normal heart there were found signs of heart disease and there was one patient with striking general arteriosclerosis with hypertension. On the whole it may be said that, although in this series the effects of the disease upon the arterial system appeared distinctly noticeable, they were hardly as severe as might have been expected.

INFLUENZA

Acute arterial lesions in influenza were described by Marmorstein (137). He reports the autopsy of a woman of 22, dead of influenza. The ascending aorta was somewhat dilated and fusiform; on the inner surface there were small islands of grayish color about twice a slarge as a pin's head. These spots were soft, the edges badly defined. The area involved measured about 1½ centimeters in diameter and there were similar plaques in the anonyma. No bacteria were found in the plaques; there was no endocarditis. There was also present thrombosis of the basilar artery and softening of the pons. Influenza bacilli were recovered from the softened brain tissue. Marmorstein seems to look upon the lesion in the brain as embolic, but there having been no endocarditis, it is quite possible that the thrombosis of the basilar artery was due to influenzal arteritis.

A case of multiple thrombotic vegetations in the pulmonary artery associated with endocarditis of the pulmonary valves with positive findings of influenza bacilli is mentioned by Welch (138) in his article on thrombosis, in Allbutt's System of Medicine.

According to the description given, the case of Cooper (139) is a very doubtful one. His own statement, "It was suggested that the condition might have been due to a circumscribed aortitis, probably influenzal in origin," is certainly very vague.

Rhea (140) called attention to a marked endarteritis of the meningeal arteries in the case of influenzal meningitis and Kuskow (141) states that endothelial lesions seem to be an early anatomical symptom of the grippe.

It is highly probable that in this disease the larger arteries are sometimes the seat of an acute arteritis, because quite a number of cases of arterial thrombosis followed by gangrene may be found in literature, at least fourteen following the epidemic of 1889–90 and over a half dozen since then. Nothing definite is known as to any permanent damage of the arteries resulting from this disease.

PYOCYANEUS INFECTION

The interesting investigations of Fränkel(142) have demonstrated that the bacillus pyocyaneus exibits an almost specific predilection for the walls of small arteries. Usually the infiltration of the arterial wall does not seem to be accompanied by any characteristic lesions, but in one case Fränkel observed a true arteritis of a large arterial branch with narrowing of the lumen of the blood vessel.

On account of the rarity of this infection it seems improbable that it should play any role in the ordinary cases of chronic arterial disease.

TYPHUS

Gangrene of the extremities or other parts of the body is not an especially rare complication in typhus and has again been observed in the course of the epidemics during the late war, as reported by Bué(143), Déléarde and d'Halluin(144), Castellani(145), and others. Déléarde and d'Halluin(144) ascribe the gangrene to a peripheral arteritis. The smaller branches of the arteries seem to be diseased, and not the large stems, as in typhoid fever, which may be due to the location of the virus in the arterioles, which has been described recently by Fränkel(146), Jaffé(147), and Nichol(148).

TUBERCULOSIS AND SYPHILIS

If chronic infections as such were to be looked upon as important causes in the development of arteriosclerosis, on account of the chronic intoxication which is always associated with them, one would imagine that there should exist a close relation between arteriosclerosis and the more common chronic infectious diseases in man, viz., tuberculosis and syphilis.

It is well known that the arteries occasionally become infected with tubercle bacilli. The disease may attack the large vessels like the aorta and pulmonary artery, or may invade the smaller blood vessels, usually from adjoining tuberculous lesions. A very typical tubercular endarteritis of the small arteries is almost regularly seen in tuberculous meningitis.

Still, on the whole, tuberculosis has not been looked upon as an important contributing factor in the development of arteriosclerosis, in fact, in this connection Rockitansky's dictum is usually cited, that the two diseases seem to exclude each other. A connection between the two, however, has been suspected by some of the French clinicians and Huchard(149) makes a very definite statement to this effect, apparently however, basing his contention upon a few isolated cases. Faber (l. c.) also emphasizes the importance of tuberculosis in the development of arteriosclerosis.

The belief that chronic syphilis is an important cause of generalized arteriosclerosis is much more widely prevalent and has again been expressed in no uncertain terms by several authors recently on the basis of general impressions or as a result of a study of the histories of such patients, but I fail to find anywhere a conclusive proof of this contention.

We are well informed in regard to the effects of syphilitic infection upon the wall of the aorta, and the luetic disease of the cerebral arteries first described by Heubner (150) forms a very definite clinical and pathological entity, but how often syphilis causes disease in other arteries, or whether it does so at all, is still an open question.

PERIARTERITIS NODOSA

At this point I may briefly state that this rare disease has not been considered by me in connection with the subject of general arteriosclerosis, because it differs in so many ways from ordinary arteriosclerosis and is almost doubtless of infectious origin.

THROMBOANGITIS OBLITERANS

The same applies to thromboangitis obliterans. The granulomatous thickening of the intima of the small arteries in this malady is so characteristic histologically that they suggest the activity of a specific virus, but the disease seems to have no relation to ordinary arteriosclerosis.

In the following I shall attempt to give an exposition of the results of my own investigations.

METHOD OF INVESTIGATION

The following presentation of the subject is based on 500 consecutive necropsies at the Lane Hospital, the teaching hospital of the Medical School of Stanford University, and in the Stanford service at the San Francisco Hospital, the municipal hospital of the City and County of San Francisco. These necropsies were performed by the author personally or by his assistants under his personal supervision. A routine gross and microscopic examination of all important viscera was made in each case, with the one exception of the examination of the central nervous system which was sometimes omitted. All otherwise incomplete autopsies were excluded from this series. Special attention was paid to the kidneys and the cardiovascular system. Each necropsy record contains a summary of the most important points in the clinical histories, but in all cases, which were of any interest at all in connection with the subject under investigation, the original clinical records were consulted. These records are quite complete, covering family history, previous history, history of present illness, clinical and laboratory findings. The latter include the usual examinations of urine, blood, sputum, etc., and in many cases Wassermann test, tests for renal function, blood urea determinations, and other special investigations. The records of patients who were brought to the hospitals very shortly before death or in an unconscious condition, or who spoke a language like Chinese, for which at times it is difficult to find an interpreter, are naturally more or less incomplete. In general it may be said, however, that most of the records were quite satisfactory both from the point of view of the clinician and that of the pathologist. I wish at this point to record my feeling of indebtedness to all those who assisted in gathering these various data in regard to the patients and particularly to the heads of the medical services, Dr. A. W. Hewlett and Dr. H. P. Hill, for their permission to make use of them.

STATISTICAL STUDY OF THE 500 CASES

All 500 cases were carefully tabulated and segregated in age groups of five years each. In the first age group from one to five years there are 115 individuals, mostly stillborn children or children who died soon after birth. In the vast majority of these cases the cause of death was congenital syphilis. As the arteries were found to be normal in all of them they were of no particular interest in connection with our special problem.

In the general statistical survey the males and females were segregated in order to test the accuracy of the general impression that arteriosclerosis is much more frequent in men than in women.

The cases of more or less general arteriosclerosis were segregated in three classes, those with slight, those with moderate, and those with severe arteriosclerosis. The lesions have been designated as slight when there were only a few scattered yellow spots in the intima, but when the blood vessels in every other respect were perfectly normal. In the group of "moderate" arteriosclerosis the intimal thickenings were more marked and more numerous. In the "severe" cases there was quite a diffuse involvement with serious disease of the entire arterial wall.

Arteriosclerosis of the aorta was tabulated separately from arteriosclerosis of the other arteries on account of the well-known fact that the lesions in these two regions do not always coincide. In the smaller arteries no attempt was made to take into account strictly the degree of involvement in different territories. The question of the special involvement of the arteries of certain organs will be considered later in connection with the different organs.

In the tabulation of lesions of the aorta the cases of syphilis of the aorta have been eliminated.

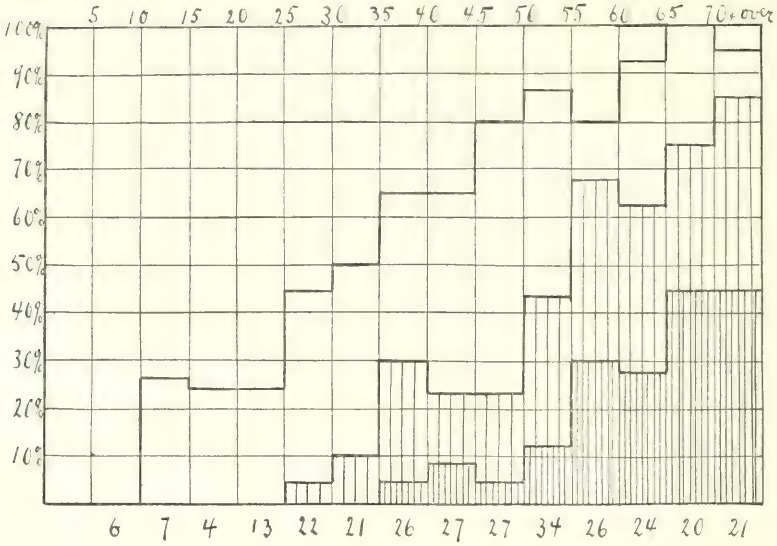
In each age group the percentage of incidence of cases of the different degrees of severity of arteriosclerosis has been calculated and entered upon the following diagrams, in which the perpendicular lines separate the age groups and the rises in the horizontal line indicate the rise in percentage of incidence of the arteriosclerotic lesions. The different degrees of severity are indicated by the shading of the fields under the line of incidence, the part of the field representing slight cases being light, that representing the moderate ones slightly darkened, and that representing the severe ones showing very dark. At the bottom of each age group is found the number of cases in each age group from which the percentage of incidence was calculated. Among the males these figures vary between 20 and 40 in the more important groups; they are, therefore, quite sufficient for a fairly accurate percentage determination. This is not the case among the females, where the numbers in the different age groups are unfortunately very low, ranging from 12 down to 2 only (in the ages between 60–70). The percentage figures among the females are, therefore, only very approximately correct.

A study of Table I brings out the following facts: Slight lesions in the aorta are seen very early, between the tenth and twenty-fifth year, and between the twentieth and twenty-fifth year they are apt to be asso-

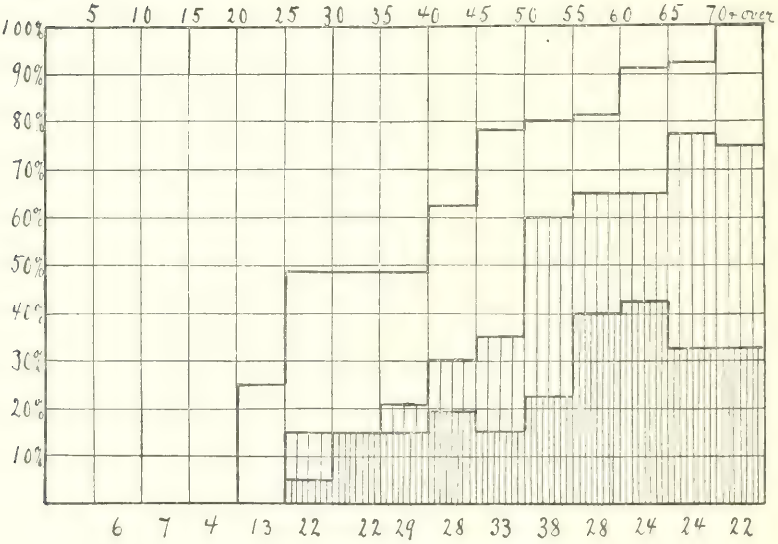
TABLE I.

Relative incidence of general arteriosclerosis in males.

a. Aorta:



b. Other arteries.



Severity of disease indicated by shading.
Figures at base line indicate total number of cases in each group.

ciated with slight lesions in the other arteries. It may be of interest to know that among the six cases which caused this early elevation of the line of incidence there are two of chronic septic endocarditis, one of chronic otitis media with brain abscess, one of subacute suppurative tonsillitis and glomerulonephritis, and one of very general chronic tuberculosis. The only non-infectious case in this group was a case of lymphosarcoma.

To return to our table: The severe forms of arteriosclerosis make their appearance in the larger arteries between 25 and 30 years of age; somewhat later in the aorta, between 35 and 40, and from then on they rise gradually to a maximum at about 65. From the age of 65 on there seems to be no more relative increase in the severe form. Table I*b* shows a reduction from about 43 per cent to about 33 per cent after 65 years of age, and this in spite of the same absolute number of cases in these later age groups. In the aorta the percentage of incidence remains stationary.

The percentage of cases with moderate arteriosclerosis varies with each age group; all the way from less than 10 to nearly 40 per cent, averaging about 30 per cent. These variations are hardly important on account of the fact that the distinction between the severe and the moderate forms is naturally somewhat arbitrary.

The combined curve of both moderately diseased and severe cases rises gradually with increasing age to the end.

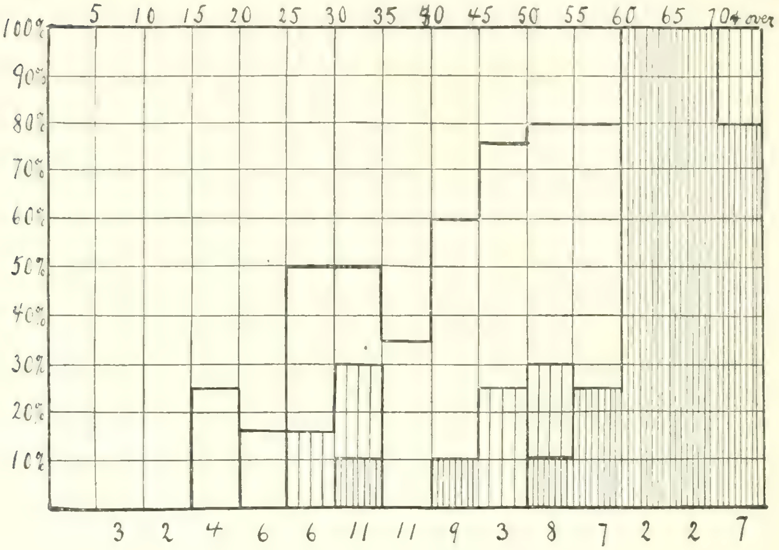
The combined curve of all three types ascends pretty much in the same way until in the age group from 65 to 70 there are no more normal aortas, and the same is true of the other arteries in this series at 70 or over. There was, however, one patient with an entirely normal aorta in this last group.

If we now compare Tables I and II we notice that in women the slight lesions in the aorta commence very nearly at the same age: at 15; and those of the other arteries at 20. The curves in Table II naturally are not so perfect as those in Table I on account of the much smaller number of cases. The drop to almost no lesions in the age group from 35 to 40 both in aorta and in the other arteries is difficult to account for except as a matter of chance. Still the rise of all three curves is not so very different from those in Table I. The tables, therefore, do not show the striking difference in incidence and extent of arteriosclerosis between male and female that is usually assumed to exist. It is probable that the statistical figures that are usually quoted are vitiated by the fact that they have not been reduced to percentages in different age groups. At all events this finding encouraged me to omit the differentiation between male and female in my other statistical calculations.

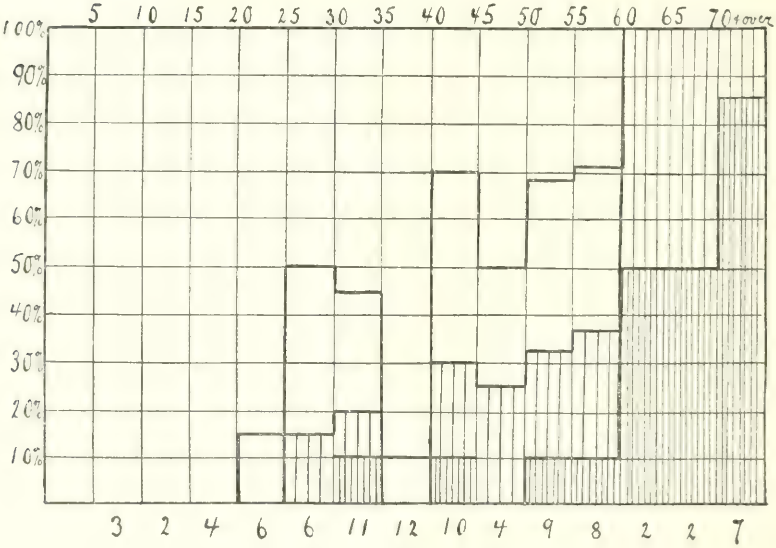
TABLE II.

Relative incidence of general arteriosclerosis in females.

a. Aorta.



b. Other arteries.



Severity of disease indicated by shading.
Figures at base line indicate total number of cases in each group.

INFLUENCE OF SENILITY

If we now look again at the more representative Table I, one could hardly wish for a clearer demonstration of the importance of age in the occurrence and development of the disease, and this, of course, is common knowledge. The question is, how to interpret this observation.

It has been suggested that age as such is a determining factor, that the gradual wearing out of the elastic and muscular elements of the arterial wall in the natural course of events gave rise to arterial degeneration ending in sclerosis; in other words, arteriosclerosis by many is regarded as a true senile change. By others certain forms of the disease have often been called "senile" arteriosclerosis in contradistinction to those types which occur earlier in life.

The question then naturally arises, What is senility, and how far is it due to natural influences, and how far to the cumulative effects of disease? It has often been said that man under present conditions dies prematurely, and that, if certain vicious influences could be removed, our natural span of life would be increased greatly. My impression gathered at the autopsy table would make me rather reluctant to accept such an idea; but fortunately for our present purpose, it is not necessary to solve this problem of the ages. All we need to do here is to ask ourselves, What sort of a curve of incidence would we expect if arteriosclerosis was altogether or even largely due to senile degeneration of the arteries? The answer to this question, to my mind, is evident: There should be a very gradual rise commencing at about 40 years of age to account for the certainly relatively few persons in whom the arteries actually wear out prematurely. This gradual rise would continue to about 55, and then there would be a sudden increase to 80 or 90 per cent, and more when we approach the time when senility makes itself felt in the average individual. It would be highly improbable that after 70 years of age there should be anyone left without well-marked arteriosclerosis.

The actual curve is very different from such a one as I have just described. It commences to rise at an age at which it is impossible to assume that the arteries of many are already beginning to wear out; it rises, not at first gradually and then very suddenly, but evenly, step by step, until a maximum is reached, and its progress appears to be rather retarded, if anything, in old age.

Unless we assume that some people's arteries are endowed with quite unusual resistance to the assumed destructive effect of old age, the fact shown by our tables, and also a matter of common observation, that very old people may have normal arteries, or arteries which are very nearly so, could not possibly be understood on the basis that the disease is the direct result of age and of the senile deterioration associated with it.

It will be objected that in this argument I am taking an extreme position in trying to eliminate from our calculation all other influences but age, that it is really the inseparable combination of disease and old age which causes the gradual rise of the curve as seen in the diagram. But before accepting this conclusion it may be well to consider what disease alone might be able to do.

INFLUENCE OF INFECTIOUS DISEASES

Could disease alone without the influence of senility produce a curve of this character, leading eventually to the involvment of the arteries of practically everyone? It certainly could, but only under the following conditions: First, that the disease or diseases affecting the arteries were very common and affected all ages fairly evenly, so that practically no one eventually would escape their influence; second, that the arteries must be much more readily susceptible to the influence of disease than is now believed to be the case; third, that the lesions produced in the arteries must develop very slowly, in the course of 10, 20, or 30 years and more. With these assumptions one can readily explain a curve of incidence as presented without having any recourse to the problematical effects of senility. Time naturally would be an important factor on account of the slow development of the lesions, but senility might not play any role at all.

What sort of arteries do we find in individuals who never have had any serious disease, particularly no serious infections? Individuals of this kind are not very common, especially among the people who frequent public hospitals, but in our series I have found fifty-one cases in which there was a fairly complete history without mention of severe infections and where no lesions suggesting a preceding severe infection were found at autopsy. It is evident that it is very difficult to be certain of such negative data and there is no doubt that patients who have had serious infections have been erroneously placed in this list. This applies particularly to individuals over 60 whose memory is apt to be more or less impaired. In spite of these limitations the statistical result as shown in Table III is quite striking.

On account of the smaller number of cases, they have been collected in this and the following tables in age groups of ten years each, but as these groups in the diagrams take double the space of the five-year groups in the preceding tables, the incidence curves are directly comparable. The cases with slight lesions have been omitted on account of their being so nearly normal.

TABLE III.

Relative incidence of general arteriosclerosis in cases without severe infections.

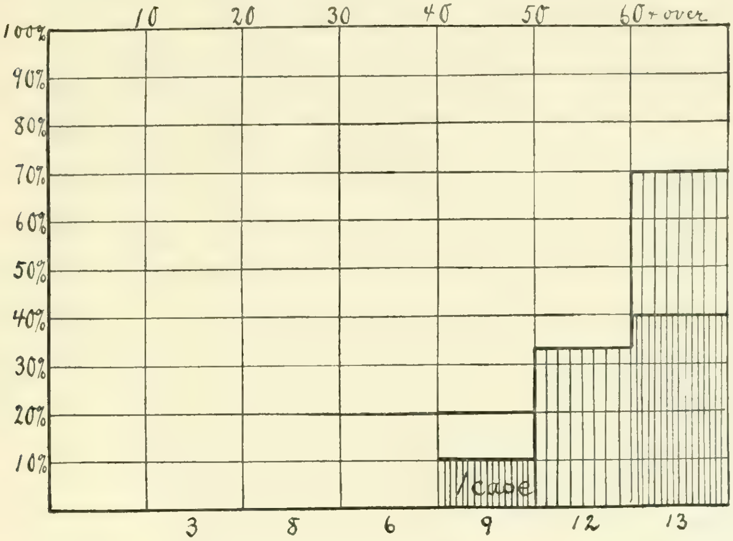


Table III shows that in this group there are no cases of arteriosclerosis before the age of 40; there is one severe case among nine between 40 and 50 (certainly an error through lack of information in the history); there are three moderate cases among twelve between 50 and 60, and three moderate and four severe cases among thirteen in persons of 60 and over. The curve is much more like that which we constructed theoretically for the possible influence of senility alone, but, although this in itself would be very satisfactory, I feel doubtful, as indicated above, whether our information is really complete enough in the cases of this group with arteriosclerosis among elderly individuals. The relative freedom from arteriosclerosis in this group is certainly very evident.

I have preferred not to group all cases with a history or other indications of severe infection in one general table, because in so doing the infections not affecting the arteries would obscure the real influence of those which might do so. I have therefore picked out a few groups of patients separately: those with a history of scarlet fever, those with a history of typhoid, the large group with septic (rheumatic) infections of various kinds, those suffering from tuberculosis, and last, those afflicted with syphilis.

In the general group of septic infections are included all patients giving a history of repeated attacks of tonsillitis, of rheumatism, of septic infections of wounds or bones, or of "malaria." This latter inclusion requires some explanation. It was found that not only patients but often their medical advisers regard any disease that is associated with chills and fever as malaria. This is true especially of the patients coming from the interior valleys of California, where malaria actually is a common disease. Careful questioning of these patients, however, frequently reveals that their trouble could not have been malaria but probably had been some form of general sepsis; in addition it is very suggestive that the diagnosis of "malaria" appears very commonly in the histories of patients suffering from septic endocarditis and other septic conditions. For these reasons it has been thought best to include all cases with this history among the septic cases. If in this way any true cases of malaria should have been included it would only vitiate the result in a negative way, because we have no reliable evidence whatever connecting malaria with arteriosclerosis. Included in this group are also all cases in which evidence of chronic sepsis was found at autopsy; especially, of course, all cases in which there were lesions resulting from chronic endocarditis.

It is often stated that arteriosclerosis as such affects the valves of the heart and may cause serious lesions in them, but I prefer to believe that if the valves are actually badly deformed, adherent to each other, thickened in places where endocarditic deposits usually occur, these changes are best interpreted as resulting from a healed endocarditis. I feel certain that in many instances the evidence in this regard is quite unmistakable. So all cases with noticeable lesions in the heart valves have been included among the septic cases. It is well known, of course, that the edges, especially of the mitral valve, are apt to be thickened more or less in later life. It is customary, therefore, among pathologists to disregard these thickenings almost entirely, with how much justification in fact it is difficult to say, but it may be stated here that in our series only those changes were counted as suggestive of healed endocarditis in which it was quite evident on close examination that they could not very well be accounted for in any other way.

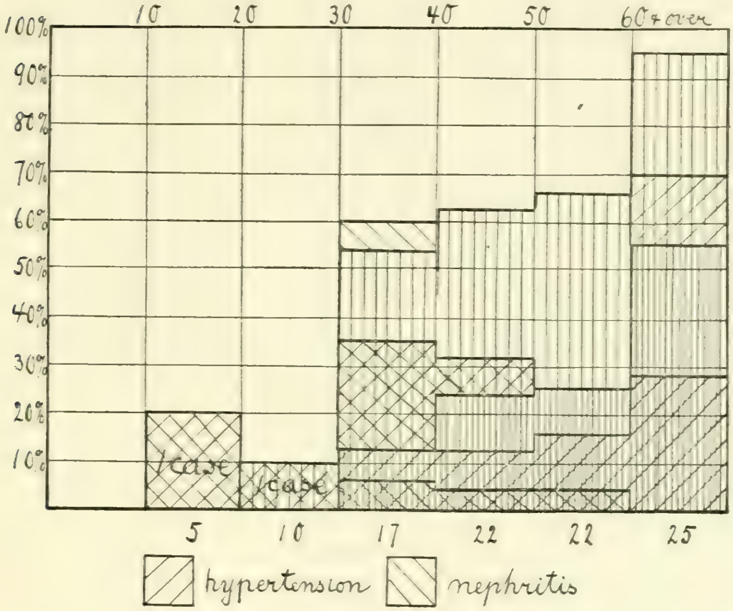
These "septic" cases are analyzed in Table IV. In this table the relative incidence of nephritis is indicated by oblique hatching from left to right, and the relative incidence of hypertension by oblique hatching from right to left.

In Table IV we find between the ages of 10 and 20 an early case of subacute nephritis without arteriosclerosis, between 20 and 30 one case of subacute nephritis with moderate arteriosclerosis, between 30 and 40 among seventeen individuals (reading from above downwards) one with subacute nephritis without arteriosclerosis, three with moderate arteriosclerosis, four with chronic nephritis, hypertension and moderate arteriosclerosis, one with marked arteriosclerosis and hypertension, and one with chronic nephritis, hypertension and marked arteriosclerosis. In the age

TABLE IV.

Relative incidence of general arteriosclerosis in septic cases

(Chronic streptococcal infections.)



group between 40 and 50 there are six cases of moderate arteriosclerosis, two cases of chronic nephritis with hypertension and moderate arteriosclerosis, two cases of marked arteriosclerosis without hypertension, two cases of marked arteriosclerosis with hypertension and one case of chronic nephritis with hypertension and marked arteriosclerosis. The conditions in age group 50 to 60 are very similar to those in the group from 40 to 50, and among the twenty-five individuals over 60 there is only one with normal arteries; the rest show moderate and severe general arteriosclerosis with a large proportion of hypertension cases. It is interesting that in our series none of the nephritis cases reached the age of 60 or more. All cases of nephritis and of arteriosclerosis with hypertension in which there is a full history appear in this group.

I believe no more convincing proof could be furnished of the overwhelming importance of chronic septic conditions in the development of both nephritis and general arteriosclerosis than is contained in Table IV, especially when contrasted with Table III; in Table III few cases in the last decades, and in Table IV many early cases, development of lesions in the majority of cases after 30 and in practically all cases after 60.

In studying the histories of these septic cases the time element in the development of disease is brought out quite strikingly. In most cases, if there is any definite record of it, the original infection dates back to childhood or early adult life. At that time the body as a whole and the arteries in particular appear to be most susceptible to the influence of infections of this character. It would also seem that from the time of injury the arterial disease develops very slowly, but progressively.

There seems to be one striking difference between nephritis and arteriosclerosis which is this: that even in the late stages of chronic nephritis we still usually find a more or less active septic focus somewhere in the body, whereas in arteriosclerosis the focus, if we find one, is practically always extinct. This fact is rather difficult to explain, but it may suggest that after the initial injury the lesions continue to develop independently of the septic process, which, of course, has been suspected by those who have seen the importance of the infection in the primary injury done by it to the vessels and have attributed the further development of the progressive anatomical lesions to the resulting deterioration of the arterial wall.

The Tables V and VI, dealing with those patients who had had an attack of typhoid fever or of scarlet fever, are not very satisfactory on account of the small number of patients in our series of whom it was known that they had had these diseases.

TABLE V.

Relative incidence of general arteriosclerosis in patients with history of typhoid fever.

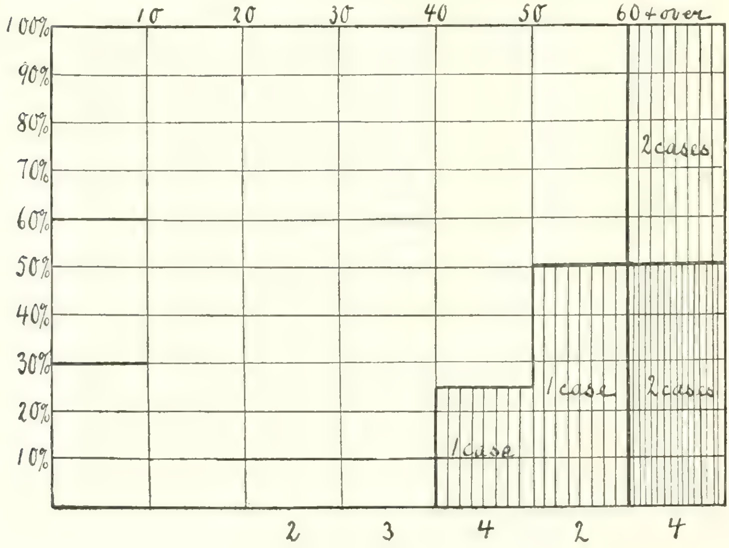
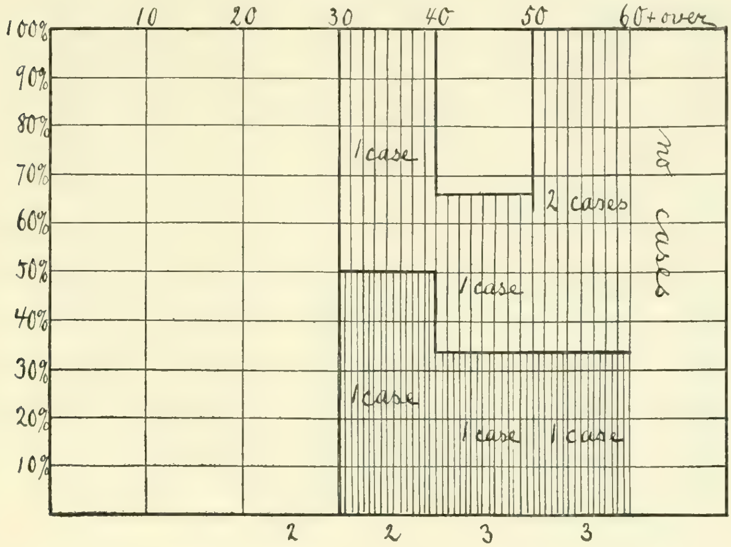


TABLE VI.

Relative incidence of general arteriosclerosis in patients with history of scarlet fever.



There were altogether fifteen patients with a definite history of having had typhoid fever. As tabulated in Table V they certainly do not suggest that arteriosclerosis is a frequent sequence of typhoid fever, in fact the resemblance of Table V to Table III is evident. This is quite contrary to expectation on account of Thayer's work and on account of the fact that acute infections of the arteries are relatively common in this disease.

Among the 500 patients studied there were only 10 who to our knowledge had had scarlet fever. The small number practically prevents successful use for statistical purposes. It might appear, however, from Table VI that scarlet fever in this connection also should be classified with the septic infections to which it belongs otherwise.

Tables VII and VIII, giving the results in tuberculosis and syphilis, are again full of interest.

There were 51 patients with marked tuberculosis, mostly with chronic pulmonary tuberculosis. Among all these patients there was only one with marked arteriosclerosis. One might say, patients with chronic tuberculosis do not live long enough to develop general arteriosclerosis, and there is certainly some truth in this statement, but the diagram seems to imply more than that. It seems almost certain from it that chronic tuberculosis has no effect upon the arteries whatsoever, at least so far as arteriosclerosis is concerned.

TABLE VII.

Relative incidence of general arteriosclerosis in patients with chronic pulmonary tuberculosis.

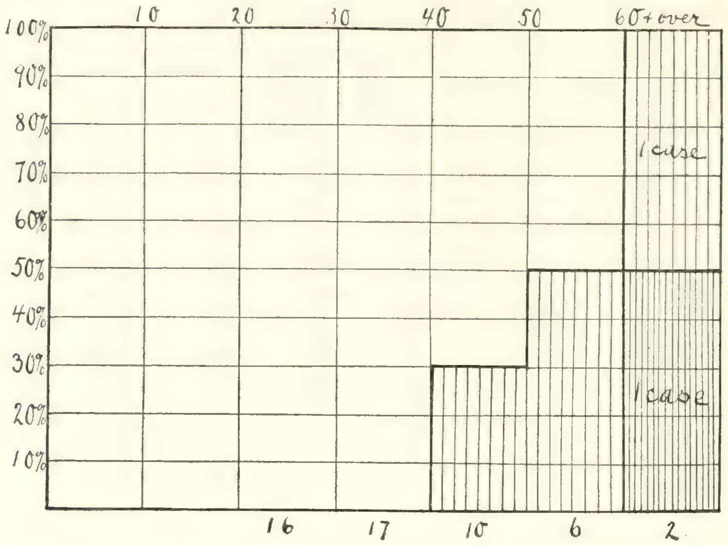
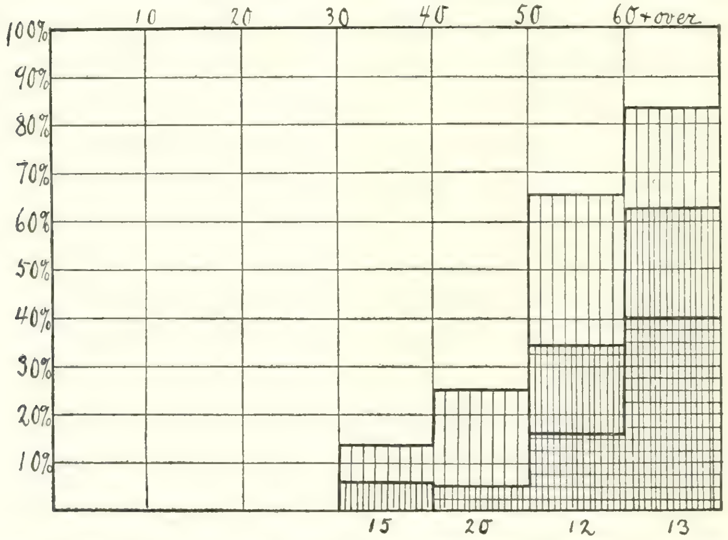


TABLE VIII.

Relative incidence of general arteriosclerosis in patients with syphilis.



Horizontal lines indicate cases in which there was also evidence of chronic septic infection.

In Table VIII, dealing with the syphilitic patients, the simultaneous occurrence of septic conditions has been indicated by horizontal hatching, because as shown this coincidence was very commonly observed, especially among the patients with severe general arteriosclerosis. The diagnosis of syphilis in these cases was made from the history or from typical anatomical lesions—among which chronic syphilitic aortitis was the most common one—or from a positive Wassermann reaction. There are very few cases, however, among these 60 patients in which the positive Wassermann reaction was the only sign of syphilis. Even with the septic cases included, as they are in the table, the influence of syphilis on the development of general arteriosclerosis is not very evident, and when these cases are eliminated the relative incidence in Table VIII would show a great resemblance to that in Table III of the cases without infections, viz., there would be only two cases of arteriosclerosis, one moderate and one marked, one between 30 and 40; four cases of moderate arteriosclerosis among 20 between 40 and 50; two cases of marked and three cases of moderate arteriosclerosis among 12 between 50 and 60, and three cases of marked and three cases of moderate arteriosclerosis among 13 at 60 and over.

There is nothing in this table, therefore, to suggest that syphilis is an important factor in the development of ordinary general arteriosclerosis.

THE RELATION OF HYPERTENSION TO GENERAL ARTERIOSCLEROSIS

In Table IX the relative incidence of *all* cases of general arteriosclerosis, both in males and females, is shown in the different age groups also of all cases of nephritis. General arteriosclerosis is indicated by the perpendicular lines, with different shading according to the severity, hypertension by oblique hatching from right to left, and nephritis by oblique hatching from left to right.

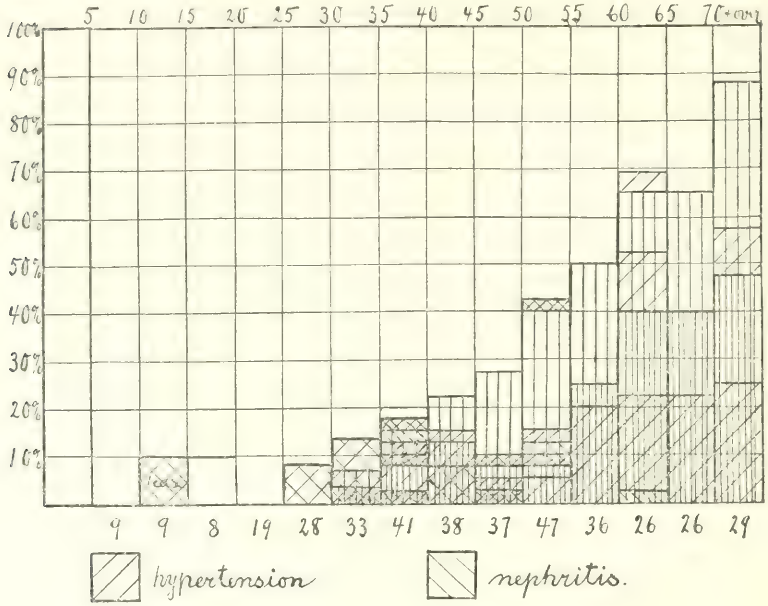
The general outline of this curve is very much like the one in Table I*b*. Probably on account of the somewhat larger number of cases in Table IX the rise is still more even.

Between 10 and 15 years there is one case of subacute diffuse nephritis in a boy of 12 with moderate hypertension and no disease of the arteries even in the diseased kidneys, excepting a few yellow spots in the intima of the aorta.

In the group between 25 and 30 years we find two cases of diffuse chronic nephritis. There was marked endarteritis in the kidneys but very little elsewhere. Both patients had high blood pressure and marked hypertrophy of the left ventricle.

TABLE IX.

Relative incidence of general arteriosclerosis, hypertension and nephritis.



Between 30 and 35 there are four cases of chronic diffuse nephritis with local endarteritis, two of these without general involvement of the arteries, one with moderate and one with severe general arteriosclerosis. The blood pressure in all four patients was high and they had a marked hypertrophy of the left ventricle.

In the next column (35–40) all possible variations are realized: marked general arteriosclerosis with hypertension, with or without chronic nephritis; moderate general arteriosclerosis with hypertension, with and without chronic nephritis; we also find one case of moderate arteriosclerosis plus nephritis but without hypertension, and one case of chronic nephritis with marked local endarteritis, no involvement of other arteries and marked hypertension.

In the next groups (40–50) in addition, cases of marked and of moderate general arteriosclerosis *without* hypertension make their appearance, and so on, until in the last column (70 and over) we find about an even number of cases of severe general arteriosclerosis with hypertension and without it, and among the cases of moderate general arteriosclerosis about 33 per cent with hypertension.

The practically complete disappearance of all cases of chronic nephritis after 55 merely indicates that these patients rarely reach a higher age.

Some of these cases are of special interest. One of them (XX–160) is that of a man 50 years of age, with a very marked old diffuse nephritis, very marked local endarteritis in the kidneys but practically normal blood vessels elsewhere. His blood pressure had always been very high, and when he died of uraemia we found a very marked concentric hypertrophy of his left ventricle. His nephritis was discovered when he was still quite young, so that his arteries must have withstood the strain of high pressure for a great many years.

In contrast to this case may be mentioned a patient, 60 years of age, with very marked general arteriosclerosis and severe nephritis, whose blood pressure remained normal and who had a normal heart at autopsy. He also died in uraemia. This last patient in addition suffered from chronic pulmonary and intestinal tuberculosis, which may have some bearing on the lack of development of hypertension.

The following case (XIX–51) is of interest because the large arteries were normal but the small arteries very severely affected. This was a man of 60 with normal kidneys, few spots in his aorta, apparently normal arteries throughout, who died with a very marked hypertrophy and dilatation of the heart. The autopsy findings were those of a clear-cut case of essential hypertension, but more careful investigation revealed a very marked obliterating endarteritis in the medium-sized branches of the splenic and renal arteries. These arteries were obliterated to such an extent that anaemic necrotic infarcts had developed in both organs. (For details see page 64.)

CASES OF HYPERTENSION WITH LITTLE OR NO ARTERIOSCLEROSIS AND NO NEPHRITIS

Among our other records, outside of the 500 used in this article, I was able to find three cases of marked chronic hypertension with little or no disease of the arteries or of the kidneys:

CASE 1. XII-52. E. B., 29 years. This patient had few small yellow spots in aorta, otherwise normal arteries, both on gross inspection and on microscopic examination of the branches in various organs, few very small scars in kidneys, healed endocarditis of mitral valves without serious deformity of valves, local healed pericarditis with adhesion at apex, very marked hypertrophy and dilatation of the entire heart, cyanotic atrophy of liver, cyanosis, general anasarca, ascites, hydrothorax.

CASE 2. XVIII-138. C. J., 40 years. In him autopsy revealed few atheromatous plaques in abdominal aorta, all other arteries normal on gross inspection, slight intimal thickening in arterial branches in spleen, liver, kidneys, heart and intestines, few small scars in kidneys, healed endocarditis of mitral and aortic valves without serious deformity of valves, marked hypertrophy and dilatation of the entire heart, few small scars in heart muscle, cyanosis, oedema of lower extremities, ascites, hydropericardium.

The third case showed more definite arterial lesions and connects up these two extreme cases with the more numerous observations in which a moderate general arteriosclerosis is associated with hypertension.

CASE 3. XIV-45. K. U., 35 years. At autopsy we found moderate atheroma of aorta, slight arteriosclerosis in coronary, pulmonary, abdominal and peripheral arteries, well marked endarteritis in small branches of renal arteries, many small scars in kidneys, moderate arteriosclerosis of small branches of coronary arteries, many small scars in heart muscle, healed endocarditis of mitral valve without serious deformity, very marked hypertrophy and dilatation of entire heart, brown induration and haemorrhagic infarcts in lung, cyanotic atrophy of liver, general anasarca, ascites, hydrothorax, hydropericardium.

All three patients showed evidence in their heart valves of preceding general septic infection. Unfortunately the clinical records of two of them (Cases 1 and 3), who died many years ago, are lost. In Case 2 the patient had had typhoid fever at 12, polyarticular rheumatism at 22, 24, and 35; he also had had attacks of "malaria." Otherwise he had been fairly well until shortly before he came to the hospital with broken compensation. He died about six months after the commencement of his decompensation.

In the present series we found nine cases in which there evidently had been present a continued high blood pressure in spite of the fact that the arteries generally were not badly diseased, nor were there any severe renal lesions. The following is a condensed record of the most characteristic one of these:

Man of 41, limited arteriosclerosis, low blood pressure, very marked hypertrophy of the heart, death from myocardial insufficiency, no etiological factor found except possibly over-exertion.

XX-172. S. F. H. 22517. J. H., 41 years, logger; entered February 14, 1917, died June 16, 1917. Family history unimportant.

Patient did not remember ever having been ill but had always done the hardest kind of work on railroads, in shipyards and logging. He denied venereal disease and the Wassermann reaction was negative. He was a heavy whiskey drinker at times, but used little tobacco. In January, 1915, he had his first attack with dyspnoea, palpitation, dry cough and oedema of the feet. This incapacitated him for five months. He eventually recovered but occasionally still suffered from palpitation and dyspnoea. An exacerbation of his previous symptoms occurred two months before he came to the hospital. This was associated with precordial pain, feverish feeling and much sweating. The pain was very severe day and night and lasted for several weeks. Later he had pains in his left arm similar to those in chest.

Clinical examination showed cyanosis, dry cough, dyspnoea of Cheyne-Stokes type. His teeth were fairly good, his tonsils small. The veins of the neck exhibited presystolic pulsation. Rales were heard at the bases of the lungs. The heart was distinctly enlarged. A systolic murmur was heard at the apex, which was transmitted to axilla and back. On the right of the sternum a to and fro murmur could be made out. The second pulmonic tone was accentuated. There were numerous extrasystoles. The blood pressure registered 128-76. The spleen was enlarged and hard. No bacteria were found in the blood, although several attempts were made to find them by blood culture. There was no oedema. The temperature was irregular, at times above normal. Eight days of high fever were observed at the beginning of May and at that time there was an increase in the leucocytes to 41,000 per cmm. The pulse rate varied very much, fluctuating between 90-120 per minute. The blood was nearly normal (5 million reds and 85% Hb.) The urine contained a slight trace of albumin, some granular casts, at times some blood. The condition of the patient changed very little, while he was at the hospital. At one time he developed slight oedema of the ankles, which, however, disappeared again in a short while. Towards the end he had several severe attacks of dyspnoea and cyanosis with feeling of impending death.

Autopsy revealed marked arteriosclerosis of the coronary and pulmonary arteries, also some arteriosclerosis of the small arteries in the spleen. The arteries of the kidney and the kidney tissue were normal. The other arteries and the aorta were normal. The heart was very markedly hypertrophied and dilated on both sides (3 x normal size). The heart valves were normal except the aortic cusps, which were very slightly thickened. Some small scars were found in the hypertrophied wall of the left ventricle. The liver showed a beginning cyanotic atrophy. There was a general cyanosis and some oedema of the lower extremities and of the lungs.

This man of 41 had a tremendous hypertrophy of the heart although his arterial disease was limited to the coronaries and pulmonary arteries and although the kidneys and their arteries were entirely normal, both in the gross and on microscopic examination. He entered the hospital with marked decompensation. His blood pressure therefore was not high at the time. There is nothing in his history or in the clinical findings to throw any light on the etiology of the process. The fact that he had always done very hard physical work can hardly be looked upon as more than a contributing factor; the slight lesions in his aortic valves and the few small scars in his myocardium may, however, suggest that at one time he may have suffered from a more or less severe general septic infection.

In the other eight cases the patients did not die of decompensation but of other conditions, partly associated with their arterial disease, as cerebral softening or haemorrhage into the brain, myocarditis or coronary thrombosis, partly independent of it, as cirrhosis or carcinoma. One patient who carried pus pockets in his tonsils died of an acute exacerbation of an old focal nephritis with acute septic pleurisy. (For details see Case XX-10 on page 73.)

Condition of Kidneys in These Cases

The condition of the kidneys in these eight cases was as follows: one had a marked atrophy of one kidney with very marked arteriosclerosis of the renal artery and its branches on that side, whereas the arteries on the other side were only moderately diseased and the kidney practically normal. The kidneys of the remaining patients contained some small scars, and in some of them the arteries were badly diseased, but not more so than in many other patients without hypertension.

All except one patient of 78 years, who died of carcinoma of the prostate, had severe arteriosclerosis in one or the other organ, but the arteries in general were in a fairly good condition.

Evidence of Preceding Infection in These Cases

In the majority of these cases there was evidence of chronic active or healed septic infection as follows:

CASE 1. XX-10. Man of 38. He had *pus pockets in tonsils,* slight atheroma of aorta, moderate general arteriosclerosis, more marked in small arteries of spleen and kidneys, many small scars in kidneys, marked hypertrophy and dilatation of the heart, cyanotic atrophy of liver. Toward the end there was observed a recrudescence of tonsillitis followed by acute glomerulonephritis. He died in uraemia. (For details see page 73.)

CASE 2. XX-22. Man of 53. He had a *healed mitral endocarditis* with moderate stenosis, marked atheroma of aorta, moderate general arteriosclerosis, many small scars in kidneys, moderate concentric hypertrophy of left ventricle. He died of cirrhosis of the liver.

CASE 3. XIX-26. Man of 60. No history. He had marked atheroma of aorta, moderate general arteriosclerosis, many small scars in kidneys, very marked arteriosclerosis of right renal artery with atrophy of right kidney, slight concentric hypertrophy of left ventricle. He died of softening of the brain.

CASE 4. XX-190. Man of 61. *History of "malaria" at 40.* He had a slight atheroma of the aorta, moderate general arteriosclerosis, more marked in branches of renal arteries, but only small scars in kidneys, moderate hypertrophy and dilatation principally of the left heart, cyanotic atrophy of liver. He died of thrombosis of left coronary artery.

CASE 5. XX-112. Man of 62. *History of tonsillitis and rheumatism.* He had *pus pockets in tonsils,* moderate atheroma of aorta and moderate general arteriosclerosis, somewhat more marked in kidneys, few microscopic scars in kidneys, moderate hypertrophy and dilatation of both ventricles. He died of haemorrhage of brain in basilar ganglia. (For details see page 60.)

CASE 6. XXI-32. Man of 70. *History of several attacks of "malaria."* He had moderate atheroma of aorta, moderate general arteriosclerosis, large scars in myocardium, few small scars in kidneys, hypertrophy and dilatation of entire heart, cyanotic atrophy of liver. He died of myocarditis. (See page 61.)

CASE 7. XXI-54. Woman of 72. Autopsy revealed *healed endocarditis of aortic and mitral valves with mitral stenosis,* slight atheroma of aorta, moderate general arteriosclerosis, small scars in kidneys and myocardium, very marked concentric hypertrophy of the left heart. She died of softening of the brain.

CASE 8. XXI-15. Man of 78. No history. He had marked atheroma of aorta, moderate general arteriosclerosis, few small scars in kidneys, marked concentric hypertrophy of left ventricle. He died of carcinoma of the prostate.

In all these cases in which there is a clinical record there is either a history of preceding septic infection or there was found at autopsy some anatomical evidence of such an infection.

CASES OF SEVERE ARTERIOSCLEROSIS WITHOUT HYPERTENSION

Another interesting group is formed by the cases of severe general arteriosclerosis without hypertension. These number 28, as against a total of 35 cases of severe arteriosclerosis without nephritis but with hypertension. A most careful examination of the clinical and of the necropsy records fails to reveal any reasonable explanation for this difference in the behavior of the blood pressure.

It has been suggested that it might be possible to distinguish in some way between the lesions in hypertensional arteriosclerosis and those of "senile" arteriosclerosis without hypertension, but this is not the case, and if we arrange the cases according to age we do not find any very striking difference in proportion. As shown in Table IX, from the age of 60 on, at least, the proportion between the two types of cases remains practically the same, whereas it should certainly change, if the "senile" cases were specially exempt.

The diagram does show, however, that severe arteriosclerosis which causes death early is usually associated with hypertension. Among the patients below 60 years who died with severe arteriosclerosis a very large proportion presented evidence of hypertension. This merely means that arteriosclerosis with hypertension is more dangerous to life than arteriosclerosis without hypertension.

That hypertension may be transitory and may disappear without leaving any traces is shown by the record of one of our cases in which we happened to be able to obtain an old history from another hospital where the patient had been examined several years before. At her first examination she had had a systolic blood pressure of 200 millimeters mercury and her diastolic pressure was 120. She then had acute attacks of very severe dyspnoea which by the physician in charge were regarded as anginal. When she came to us her blood pressure was normal. Autopsy revealed a marked atheroma of the aorta, a very marked general arteriosclerosis, many small and some larger scars in her kidneys and *a heart of normal size.* She died of carcinoma of the gall bladder.

It appears not at all unlikely that of the other cases of severe arteriosclerosis without hypertension some may have suffered from more or less transitory attacks of hypertension which would not necessarily be associated with such violent symptoms and therefore would be likely to escape the attention of the patients or even of their attending physicians.

Even a continued hypertension may fail to produce a definite hypertrophy of the heart. This seems to be shown by the following case:

XX-47. A diabetic, 39 years of age, who had had signs of diabetes for sixteen years, developed diabetic gangrene of both legs and died in coma after one of the operations necessitated by this condition. This man had a severe chronic nephritis with still fairly good phenolsulphonephthalein excretion; he had a moderate general arteriosclerosis and a very severe arteriosclerosis in the arteries of his lower extremities. He was in the hospital for six months and during this time his blood pressure was about 180 mm. mercury systolic and 80 diastolic. Clinically he had a heart of normal size; a systolic murmur was heard in the aortic area. At autopsy the heart was found to be normal in every way.

Kidney Findings in These Cases

A comparison of the findings in the kidneys in the cases with and without hypertension reveals that there were large scars in the kidneys in about 47 per cent of the cases with hypertension and in about 32 per cent of the cases without hypertension. This is certainly not a very striking difference. The rest of the cases of both types had sometimes few, sometimes many, small scars in the renal cortex. The branches of the renal arteries were more or less involved in all cases and careful microscopic examination did not reveal an especially marked involvement of the renal arterioles in hypertension cases. In fact, they may be severely diseased in both types of cases. The only entirely normal kidney was found in a patient of 41 with tremendous hypertrophy of the heart and very little disease in the arteries.

From the data at hand I believe one may safely conclude that the condition of the kidneys or the degree of arteriosclerosis in the renal vessels, large or small, does not play an important role in the production of hypertension in these cases. From this, I think, also follows that even in diffuse nephritis with hypertension it is not the condition of the kidneys or of the arteries in them which causes the hypertension. This is all the more probable in view of those cases of chronic nephritis in which the functionating kidney tissue is nearly totally destroyed and in which still there is no hypertension.

The course and final termination of the disease in severe general arteriosclerosis vary very much in the different patients. There are a great many persons with advanced arterial disease in whom only a careful clinical examination reveals any abnormality of their cardiovascular system. Such is the case most commonly in people with general arteriosclerosis without hypertension, and a considerable proportion of them die of intercurrent disease and the disease of the arteries represents only a finding of minor importance.

The large proportion of such individuals who die of carcinoma or other malignant disease is quite remarkable. In our series this happened in about 50 per cent of all cases of severe arteriosclerosis without hypertension. Even taking into consideration that we are naturally dealing with persons well advanced in years, this large number of cancer cases is quite startling.

It may be, after all, that on account of its debilitating influence malignant disease does prevent the development of hypertension, and for this reason is found to be present so frequently in these cases. The only other fairly reasonable suggestion that offers itself is this: that these individuals suffer from a fundamental, probably inherited, lack of vitality which prevents the occurrence of hypertension and at the same time predisposes to malignant disease.

Among the remaining patients of this group without hypertension who did not die of carcinoma there were several who had severe lesions resulting from arteriosclerosis either in the myocardium or in the brain.

This group of cases of severe general arteriosclerosis without hypertension consists altogether of 28 patients, of whom 14 died of carcinoma, five of the remaining 14 had marked obstruction of the coronary arteries, which had been followed by thrombosis and myocardial necroses in two. In four of the five cases of coronary obstruction there were scars in the myocardium. Two patients had severe lesions in the cerebral arteries with areas of softening in the brain. The rest of the patients died of mitral stenosis (1), chronic septic endocarditis (1), chronic pulmonary tuberculosis (2), hyperthyroidism (1), diabetes (1), meningitis (1), prostatic hypertrophy (2), and there was one death from pulmonary embolism following a surgical operation.

SEVERE GENERAL ARTERIOSCLEROSIS WITH HYPERTENSION

The cases of severe arteriosclerosis with hypertension may be subdivided into two groups: the compensated ones, in which the disturbances in the general circulation are comparatively slight, and the decompensated ones, which exhibit the usual signs of chronic heart disease and often die as a result of decompensation.

The first group of patients with compensation comprised 26 individuals; of these ten died with lesions caused by their arterial diseases as follows: thrombosis of coronary artery (1), myocardial scars (1), cerebral haemorrhage (4), and cerebral softening (4). Two more of these patients died in coma, for which no explanation was found at autopsy in the condition of the kidneys or that of the brain. The rest died of intercurrent diseases as follows: pneumonia (1), gangrene of lungs (1), chronic pulmonary tuberculosis (1), syphilitic aortitis with aneurism (1), leprosy (1), malignant disease (2), cirrhosis (3), diabetes (1). In three patients death resulted from surgical operations. Patients of this kind naturally are poor surgical risks.

The blood pressure in these compensated cases varied from 150–100 to 244–200. This latter rather high pressure was observed in a man of 60 who was brought to the hospital in a comatose condition. The autopsy revealed a large area of softening in the region of the right internal capsule, a small old apoplectic cyst in the right side of the pons. His arteries were very much diseased everywhere. The branches of the renal arteries were badly affected, but there were only a few small scars in the kidneys. The left ventricle exhibited a very marked concentric hypertrophy and in the hypertrophied muscle there were a few small scars.

Seventeen patients make up the group of decompensated hypertension cases; of these eleven died as a result of the decompensation, two from cerebral haemorrhage, one from multiple softening of the brain, one from acute nephritis, and two from advanced pulmonary tuberculosis.

The blood pressure in the decompensated cases was high in a good many, ranging from 154–110 to 210–140, but there were quite a few in which, as a result of the decompensation, the blood pressure had decreased to or even below normal. The lowest blood pressure was found in a man of 51, with marked general arteriosclerosis, many small scars in the kidneys, few small scars in the myocardium, whose blood pressure for a time registered 90–62 but later rose to 125 systolic. He eventually died of decompensation and his heart was found to be very much hypertrophied and dilated.

There are no cases in our series in which the general arteriosclerosis is not associated with more or less severe changes in important viscera like the myocardium, or the kidneys, which naturally modify their course considerably. It is therefore impossible to tell exactly what course an entirely uncomplicated case of general arteriosclerosis with hypertension would take, but the observations in which the involvement of these other organs is slight seem to show that the condition would probably be tolerated for a great many years before any serious disturbances would arise, so much so that the patients would be likely to reach advanced old age. In the end there would be signs of decompensation with periods of exacerbation and remission, but the fatal issue would probably not be long delayed after the first serious break in compensation.

The final result of our investigation as to the relation of general arteriosclerosis to hypertension is this: that in our series, among 45 cases of moderate general arteriosclerosis there were eight with hypertension (about 17½ per cent)—five of these with compensation and three with decompensation, and among 63 cases with marked general arteriosclerosis, 35 with hypertension (about 57 per cent)—21 of these with compensation and 14 with decompensation. It is evident, therefore, that hypertension is more frequently associated with severe arteriosclerosis, although the percentage of severe general arteriosclerosis without hypertension is quite considerable (43 per cent). The degree of severity of the general arteriosclerosis does not seem to have any effect on the degree of functional disturbance because the relative proportion of the compensated and decompensated cases is about the same (5:3 in moderate arteriosclerosis with hypertension and 21:14 or 3:2 in severe general arteriosclerosis with hypertension).

From all this it is quite evident that the anatomical changes in the arteries are only very loosely connected with the functional disturbance in the general circulation, which can be best explained by the assumption that they are both the possible result of one and the same cause, which sometimes might provoke more or less general arterial spasm and in this way force up the blood pressure, at other times might actually injure the walls of the blood vessels, causing anatomical changes, and in a certain proportion of cases would do both in varying proportion.

In this connection the experimental work of Läwen and Dittler(151) is of considerable interest. They tested the effect of toxins of various bacteria upon the blood vessels of frogs, using the detached posterior part of the body, including the pelvis and posterior extremities, for this purpose. They observed that the filtrates of staphylococcus cultures particularly, but also those of cultures of colon and typhoid bacilli, caused the blood vessels to contract; at the same time they observed oedema as a result of increased permeability of the walls of the capillaries. Similar results were obtained in using the surviving posterior halves of cats or rabbits. In these also a rather rapidly developing vasoconstriction was observed following infusion of the toxins by way of the abdominal aorta.

In conclusion, then, it may be stated that there is evidently some connection between general arteriosclerosis and hypertension, but that the exact relation of one to the other has not been definitely determined. It is suggested that both may result from the effects of bacterial toxins on the blood vessels, which, according to circumstances, may at times produce more of a functional, at times more of an anatomic effect, or both simultaneously.

IMPORTANCE OF ARTERIOSCLEROSIS IN VARIOUS ORGANS

In looking over our records one is at once impressed with the fact that the course of the disease and the final outcome are greatly modified according to the more or less severe involvement of different organs, and in the following an attempt is made to segregate the cases accordingly and to see how far it is possible to obtain a definite separate picture of these different types. Table X gives a general idea of the incidence of these various conditions in our series.

TABLE X

Various combinations of lesions of heart, brain, kidneys, and of gastro-intestinal tract observed in 81 cases of general arteriosclerosis and their relation to hypertension.

	hypertension	myocarditis				nephritis					cerebral lesions		gastro-intest lesion	Total
hypertension	8	15	3	2		16	2	4		1	5			56
myocarditis		15	3	2	10		2			1				33
nephritis						16	2	4	1	1				24
cerebral lesions				2				4		1	5	3		15
gastro-intest. lesions			3						1				8	12

Read from above downwards as: 8 cases of hypertension; 15 cases of hypertension and myocarditis; 3 cases of hypertension, myocarditis and gastro-intestinal lesions, etc.

In this table the cases are segregated in five groups:

1. Cases of uncomplicated hypertension (8).

2. Cases with myocardial lesions (33). Twenty-three of these patients also had hypertension; two of these 23, in addition, nephritis; three, in addition, lesions of the brain; and three, in addition, ulcers of the stomach or duodenum. In one patient there were simultaneous lesions in myocardium, kidneys, and brain. In ten cases the heart muscle was diseased, but the blood pressure was not altered.

3. Cases with severe renal lesions (24). Among these hypertension was present in 23; four of these patients had brain lesions (mostly haemorrhages); in one a gastric ulcer had developed. Three patients with chronic nephritis and hypertension also had lesions of the myocardium and one of these also of the brain.

4. Cases with lesions of the brain (18). Fifteen of these patients also had hypertension; four of these 15, in addition, had chronic nephritis; one, in addition, lesions of the heart muscle. Another three had changes in the heart, but no severe lesions of the kidneys. In three more cases there were lesions of the brain without hypertension.

5. Cases with ulcers of the stomach or duodenum (12). Three of these patients also had hypertension and myocardial lesions. One patient

of this group, who also had marked renal lesions, did not have any hypertension. Eight patients had gastric or duodenal ulcers without other marked lesions referable to arteriosclerosis elsewhere.

I shall discuss first the group with lesions of the coronary arteries and of the myocardium, because in them the disturbance is still limited to the cardiovascular system.

RELATION OF ARTERIOSCLEROSIS TO DISEASE OF THE CORONARY ARTERIES AND OF THE MYOCARDIUM

These cases may be conveniently subdivided into two groups:

1. Those in which the coronary arteries become entirely obstructed by thrombosis with development of large necrotic areas or large scars in the myocardium, and

2. Those in which the coronary arteries are merely narrowed and in which smaller lesions are found in the myocardium. In the former group hypertension seems to be relatively rare (2 out of 6 cases). Sometimes in these patients the arteriosclerosis is almost entirely limited to the coronary arteries. In the second group hypertension is apparently relatively frequent (19 out of 24 cases).

One of the patients of the first group (XX-117) died immediately following the thrombosis. He was a man of 61 with marked atheroma of the aorta, and with marked general arteriosclerosis without hypertension. The arterial disease was most marked in his coronary arteries; his right coronary being almost occluded by the thickening of the wall. Many small scars were found in the wall of the left ventricle and his sudden death was caused by thrombosis of the left coronary artery. This man had been suffering from obscure attacks of gastric pain for many years. His distress was evidently due to the gastric form of angina pectoris, but on account of the similarity of the symptoms to those of gastric ulcer a gastro-enterostomy had been performed.

Another patient (XX-190), 61 years old, for several years had had typical anginal attacks associated with dizzy spells and severe headaches. He had been much troubled with palpitation of the heart. For ten years he had been short of breath and his feet had been oedematous at times. While in the hospital he was noisy, had hallucinations and then became comatose. While in coma he was evidently in great pain. Autopsy revealed a slight atheroma of the aorta, a moderate general arteriosclerosis which was somewhat more marked in the kidneys, a moderate hypertrophy and dilatation of the heart. The proximal end and the main branches of the right coronary artery were only moderately thickened; the left coronary artery was more severely diseased, and the proximal 2 cm. were filled with a recent thrombus. Small old scars were present in the wall of the left ventricle and large irregular necroses in the posterior wall of the right ventricle.

The death of the third patient (XX-153) was also quite dramatic. He was a man of 51 years, who had always enjoyed especially good health. Suddenly he had a severe attack of angina with arrhythmia and low blood pressure which prostrated him. He died on the ninth day, after having had several more severe anginal attacks. At the necropsy we found a purely local arteriosclerosis of the arteries of his heart with thrombosis of the left coronary and a large area of recent necrosis in the posterior wall of the left ventricle.

Death occurred similarly, quite unexpectedly, in a fourth patient (XX-145). He had been a physician, 49 years of age, who had suffered from diabetes mellitus for a considerable time, and who died quite suddenly without symptoms explaining such a sudden death. He had a moderate general arteriosclerosis without hypertension and a very severe arteriosclerosis of his coronary arteries. With the microscope we discovered numerous small areas of necrosis in the wall of his left ventricle which were evidently due to thrombosis of smaller branches.

That life, however, sometimes may continue for a considerable period in spite of such severe lesions of the coronary arteries and of the myocardium is shown by the last two observations in this group.

One of these patients (XX-42) was a relatively young man of 56 who had a severe atheroma with ulceration of his aorta but comparatively little in most of his arteries except in his coronaries, which were badly diseased. Many small scars were found in the wall of his left ventricle. A large scar 5 cm. in diameter, taking in practically the entire thickness of the wall, was present in the posterior wall of the left ventricle. The left coronary artery was occluded by an old organized thrombus. The patient died as a result of a recent thrombosis of his right coronary artery. Unfortunately no history was obtained in this case.

The last patient (XX-104) was a man of 80, who came to the hospital in a comatose condition, and in whom we found a large calcified scar in the posterior wall of the left ventricle as a result of an old thrombosis of the horizontal branch of the right coronary artery. He had a very marked general arteriosclerosis and a marked hypertrophy of the left ventricle. In this case also no history could be obtained on account of the condition of the patient.

These observations show that thrombosis of the main branches of the coronary arteries is usually followed by death within a relatively short time preceded by very violent functional disturbances of the character of an angina pectoris. Some of these patients have had premonitory anginal attacks. A few may survive to die later of thrombosis of other branches or of their general arteriosclerosis. Especially in younger individuals the arterial disease may be closely limited to the coronary arteries.

In one exceptional case (XX-21) an old thrombosis with complete obstruction of the stem of the left coronary artery was accidentally discovered at autopsy. There had not been any preceding cardiac symptoms and there were no lesions in the myocardium. Both coronaries were markedly sclerotic. The patient died of a ruptured abdominal aneurism. In this instance the heart muscle must have been adequately supplied with blood by way of the right coronary artery alone. This is evidently possible in some hearts, because I have seen several instances in which, as a result of congenital malformation, the left coronary artery was very poorly developed, consisting of a very narrow tube that was somewhat difficult to detect on dissection. The heart muscle in these cases was perfectly normal; it must therefore have received its blood supply practically entirely from the right coronary artery.

Large scars in the myocardium not due to complete blocking of the coronary arteries naturally will produce similar functional disturbances, although as a rule they are not so severe.

In our series such lesions were observed in two patients.

In one of these (XXI-89), a man of 56, the condition was somewhat complicated by the presence of a chronic septic endocarditis with mitral stenosis. The right coronary artery was much thickened, but only partly obstructed. There were large scars in the anterior and posterior wall of the left ventricle with thinning and bulging. The patient complained of palpitation. His pulse was regular. He died suddenly and unexpectedly.

In the other patient (XIX-51), a man of 60, the stems of the coronary arteries were normal, but some of the smaller branches showed a marked endarteritis. In the anterior wall of the left ventricle there was a large scar. The patient complained of palpitation and anginoid pain. He died of decompensation.

Two questions, mainly, arise in connection with the smaller scars which we find comparatively often in the myocardium: one as to the relation of these scars to partial blocking of the coronary arteries by arteriosclerosis, the other as to the functional disturbances arising from them.

So far as the former question is concerned, it is usually taught that the majority of such scars, if not all of them, arise from malnutrition of the musculature at places somewhat removed from the main blood supply, where ordinarily the circulation is just sufficiently maintained to meet the requirements, but where it becomes insufficient, when by the partial blocking of the coronary arteries the blood supply is cut down below a certain necessary minimum. As a result the muscle degenerates and eventually dies and its place is taken by scar tissue.

According to our own observations this teaching seems to be fairly sound. The scars are situated usually in the anterior wall of the left ventricle and in the septum near the apex, i. e., in the region of the terminal ramifications of the right coronary artery and the coincidence of these lesions with an arteriosclerotic thickening of the wall of this artery with partial obstruction is so frequent that it can hardly be looked upon as a mere matter of chance.

There are, however, exceptions in which the main stems of the coronaries are normal and the arteriosclerotic lesions are discovered microscopically in the smaller branches. On the whole, however, these small branches do not show a marked tendency to arteriosclerotic thickening.

There are also cases in which one finds scars without any gross or microscopic lesions in the coronary arteries. Such scars, no doubt, result from healed true myocarditis. I believe that this occurs more commonly than is generally acknowledged and that this disease may lead to quite extensive scar formation in the myocardium. This is especially so in cases of general streptococcal infection with or without endocarditis.

The functional importance of the less severe changes in the coronary arteries and in the myocardium has been the subject of much debate. Krehl * and Romberg (l. c.) believed that, by a particularly careful microscopical examination of the myocardium in cases of heart disease with decompensation, they had proved that such anatomical changes in the myocardium did play an important role in causing decompensation. This contention, however, is very positively contradicted by Aschoff and Tawara,** who examined as many as 112 decompensated hearts in a similar thorough manner, and who came to the conclusion that, perhaps with the one exception of diphtheritic myocarditis, the myocardial insufficiency cannot be explained by the presence of lesions that are demonstrable anatomically. I believe they should also have excepted the severer forms of chronic myocarditis in rheumatism and chronic sepsis, because I have seen several cases of primary insufficiency and dilatation of the left ventricle with compensatory hypertrophy on the right side of the heart resulting from this cause.

Otherwise our series shows that among 27 cases of hypertension with compensation there were nine with these minor lesions in the coronaries and in the myocardium (33 per cent), whereas among 17 cases of hypertension with decompensation there were 12 such (70 per cent). In our series, therefore, coronary and myocardial disease was much more commonly observed in the decompensated cases, which might suggest that, after all, even comparatively trifling changes in the coronaries or in the myocardium or in both may be of more functional importance than Aschoff and Tawara are inclined to concede.

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* Krehl. Beitrag zur Kenntnis der idiopatischen Herzmuskelerkrankungen. Deu. Arch. f. Klin. Med. **48**, 414, 1891.

** Aschoff and Tawara. Die heutige Lehre von den pathologisch-anatomischen Grundlagen der Herzschwäche. Jena. Fischer, 1906.

Decompensated cases of this kind present the clinical picture described by Christian * in his interesting article on chronic myocarditis. In only one-half of his cases did Christian observe clinical signs of hypertension. He is, therefore, inclined to minimize the importance of hypertension in the causation of the symptom complex described by him. All of his patients, however, had enlarged hearts. Coronary sclerosis was present in about one-half of his cases. The most common anatomical lesion of the heart muscle consisted in an increase in the interstitial connective tissue, "but in numerous cases the heart muscle seems practically normal except for hypertrophy of the fibres."

I personally should be inclined to conclude from the existence of a hypertrophy of the heart, that his patients must have suffered from continued hypertension at one time or another, because with the exception of valvular lesions—which were not present—this is the only condition which can reasonably explain the hypertrophy of the left side of the heart—which was said to have been present. There is considerable evidence in the history of the patients in our present series that hypertension may disappear in the later stages of the disease, not only during the actual periods of severe decompensation, but even in the intervals during which the heart muscle does succeed in maintaining at least a semblance of compensation. These periods, of course, usually do not last very long. My position then would be, that in cases like those described by Christian, we are justified in assuming the previous existence of hypertension, until such time as we learn of some other definite new cause of myocardial hypertrophy and that they represent decompensated hypertension cases rather than cases of primary disturbance of the myocardium.

SELECTED CASES OF GENERAL ARTERIOSCLEROSIS WITH HYPERTENSION

The method of summary consideration of groups of cases followed largely in the preceding parts of this article is quite likely to lead to misconceptions unless it is used very cautiously. The individual case, however, if carefully observed clinically and thoroughly investigated anatomically, is perfect and complete in itself, and not so subject to erroneous

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*Christian, "Chronic myocarditis", *Jour. of Am. Med. Assoc.*, **70**, 1909, 1918.

interpretation. For this reason I append the condensed records of a number of selected cases of general arteriosclerosis with hypertension, with or without myocardial lesions.

I. *Three Compensated Cases: Death from Intercurrent Disease*

(1) (XX-21, S. F. H. 19767.) Man of 67 with old syphilitic aortitis, ruptured abdominal aneurism, marked general arteriosclerosis, moderate hypertension and moderate concentric hypertrophy of left ventricle, marked renal arteriosclerosis.

W. L. B., 69 years, American engineer; entered September 2, 1916, died September 5, 1916.

Patient had typhoid fever in 1903, rheumatic gout for a number of years preceding 1911, otherwise he had always been well. He denied venereal infection. He did not use any alcohol, but used tobacco moderately. Last July 4th he had a severe automobile accident with fracture of the clavicle and injury to head and shoulder. On August 26th he was awakened from sleep by severe pain in abdomen, which pain had persisted ever since.

Clinical examination showed emaciation, enlargement of supra-clavicular lymph glands, sclerosis of the radial arteries and of the arteries of the legs, pulsating tumor in upper abdomen, hard mass in upper pole of left testicle, ankylosis of the great toes. His blood pressure was 160-125. Temperature and pulse were normal. Nothing abnormal was found by blood examination. The Wassermann test was strongly positive. The urine contained much albumin, many hyaline and granular casts.

The autopsy revealed emaciation, anaemia, old fracture of left clavicle, general lymphadenitis, moderate ascites, very old syphilitic aortitis with calcification and large atheromatous ulcers, ruptured aneurism of abdominal aorta, marked general arteriosclerosis with calcification, old thrombosis of left coronary artery without myocardial lesion, moderate concentric hypertrophy of left ventricle, very marked arteriosclerosis of branches of renal arteries involving arterioles, many small scars in kidneys, chronic gouty arthritis of basal joints of great toes.

(2) (XX-41, S. F. H. 19909.) Man of 56, cirrhosis, marked general arteriosclerosis and cardiac hypertrophy, very slight involvement of arteries in the kidneys and of renal tissue.

F. M., 58 years, German laborer; entered hospital September 12, 1916, died October 9, 1916.

Family history unimportant.

Personal history: Patient had the usual infections of childhood including scarlet fever. At the age of 16 he had pneumonia, 12 years ago he had an attack of diarrhoea assoociated with pain in the stomach and in the region of the heart and at that time he was told by a physician that he had an enlarged stomach and liver. Occasionally he had been troubled with muscular rheumatism. For the last five or six years he got up once or twice at night to urinate. He voided large quantities of urine. He denied venereal infection and the Wassermann test was negative. During the last year, occasionally, an itching eruption resembling hives would appear on his skin. About two months ago oedema first showed on his legs and gradually extended upwards, eventually involving scrotum and abdomen. He also noticed dyspnoea on exertion.

Clinical examination showed scratch marks and crusts on skin, slight icterus, poor teeth, normal tonsils, some impairment of resonance and some rales at the bases of both lungs, marked enlargement of the heart-dullness, a soft systolic murmur at the apex which later became louder, distended abdominal veins and marked ascites, marked oedema of genitals and slight oedema of legs. The liver projected about three finger-breadths below the costal margin, was very hard. The spleen was palpable and hard. The pulse was somewhat irregular and variable between 90 and 120. The temperature curve was irregular and slightly elevated. The maximum quantity of urine secreted was 1000 cc. At first the urine was normal, later it contained albumin and casts; 70% of phenolsulphonephthalein was secreted in two hours. There were 4½ million red blood corpuscles in one cmm. of blood and 16,000 leucocytes with 84% of neutrophilic cells. No bacteria were found in the blood culture. He was tapped several times in frequent succession and large quatities of fluid withdrawn which at first was clear, later became chylous. Patient gradually became worse and died in coma.

Autopsy revealed chronic gastritis, cirrhosis, ascites, moderate oedema of extremities, genitals and trunk, marked general arteriosclerosis including aorta, moderate concentric hypertrophy of left ventricle, fatty degeneration of heart, partial obstruction of right coronary artery, broncho-pneumonia. The small arteries in the kidneys were only slightly involved and there were few small scars in the renal cortex.

(3) (XX-110, S. F. H. 22315.) Man of 65, marked general arteriosclerosis, moderate hypertrophy of left ventricle, history of syphilis and of chronic rheumatism, death from pulmonary gangrene during an acute attack of rheumatism.

C. H. T., 65 years, cook; entered February 2, 1917, died February 19, 1917.

Family history unimportant.

Personal history probably incomplete because patient had been a confirmed alcoholic all his life and entered the hospital in a semi-comatose condition. It was ascertained, that the patient had had a chancre 40 years before, which apparently had been poorly treated. He also acknowledged having had gonorrhoea several times. Following his syphilitic infection he suffered from rheumatism. He had had "malaria" about 20 years ago. Ten years ago he had a stroke of paralysis which lasted one hour and since then he had had numerous epileptiform attacks which involved the right side of face and both legs and arms. About one month ago he came from Stockton to San Francisco in a fit of amnesia following a prolonged debauch. Soon afterwards he had a severe attack of rheumatism in his left ankle, also a bad cough with much expectoration. There was nothing in his history to suggest a general disease of his circulatory system. For a considerable time he had had to get up two or three times at night to urinate and lately more frequently.

Clinical examination showed semicomatose condition, poor teeth, dullness and rales at the bases of both lungs, much cough and profuse expectoration. The heart appeared to be of normal size and there were no murmurs. The radial arteries were thickened and beaded. His pulse varied between 90–120. His temperature curve was very irregular, the temperature varying between 97-101. A blood count showed 34,000 leucocytes of which 82% were neutrophilic polymorphonuclears. He had incontinence of bladder and no urine was obtained for examination. There were large sores on his back. The right shoulder and left ankle were very red and swollen, painful on manipulation. The right arm and right leg were slightly paralyzed. Some blood was found in his stools. Before death he became quite delirious.

Autopsy revealed poor teeth, secondary anaemia, and marked emaciation, marked general arteriosclerosis including the cerebral arteries, no focal lesions in brain, marked arteriosclerosis of the small arteries in kidneys including some arterioles, moderate number of small scars in renal cortex, moderate hypertrophy of the left ventricle, emphysema, purulent bronchitis, broncho-pneumonia, gangrene of lung, purulent arthritis of left sterno-clavicular, the right shoulder and the left ankle joints due to infection with diplo-streptococci, moderate hypertrophy of prostate, decubitus.

In all three cases the patients had not noticed any cardiac symptoms, but clinical investigation revealed hypertension in Case 1, enlargement of the heart in Case 2, and sclerosis of the superficial arteries in Case 3.

II. *Severe Early Case, Sudden Death from Heart Failure*

(XX-65, 21017. S. F. H. 46900, L. H.) Man of 40, very marked general arteriosclerosis, with tendency to thrombosis in renal arteries, infarcts in kidneys, hypertension, marked concentric hypertrophy of heart, sudden death, many attacks of tonsillitis and rheumatism, syphilis.

J. H., 40 years, teamster and car conductor; entered November 15, 1916, died November 26, 1916.

Family history unimportant.

Personal history: Patient had the ordinary infectious diseases of childhood. At 15 he had rheumatism of his left elbow joint which left the use of his arm somewhat impaired. He had had many attacks of tonsillitis. He had an attack of pleurisy when he was 30. He had night sweats at times. Occasionally he had been troubled with palpitation of the heart. For years he had had to get up at night four or five times to urinate. About three years ago he first noticed oedema of the feet. He had had gonorrhoea at the age of 22 and chancre at 25. The syphilitic infection had been treated very poorly. He was a heavy drinker. In 1912 he had a syphilitic eruption and eczema of his hands. He was then treated with mercury and salvarsan. In October, 1916, he returned complaining of the same symptoms. At the same time he also had a marked seborrheic dermatitis. He was again treated with salvarsan and mercury.

Clinical examination showed in addition to the lesions in the skin a general enlargement of the lymph glands, a heart of normal size, a soft systolic murmur at the apex and sclerosis of the peripheral arteries. Urinalysis revealed a slight trace of albumin and a few hyaline casts. While under treatment he developed an acute tonsillitis and was sent to the hospital. There it was noticed that he had aged prematurely, that his teeth were very poor, that there were definite signs of acute follicular tonsillitis, that his heart was slightly enlarged, that there were inconstant murmurs at the apex and in the aortic area and that there was a rather wide area of dullness over the upper part of the sternum. His left testicle was small and tender. His peripheral arteries were distinctly thickened. His liver was somewhat enlarged. His heart beat was regular. There was no oedema. His blood pressure registered 154-110. The Wassermann reaction was still strongly positive. His urine at this time again showed a trace of albumin; no casts were found. The haemoglobin percentage of the blood was 70 and he had a leucocytosis of 16,000 with 90% polymorphonuclear neutrophilic leucocytes. His temperature varied between 100 and 101° F. and his pulse rate between 100 and 120. On November 17th there was observed a slight inflammation of several joints, which subsided quickly. On November 21st he complained of pains in the fingers of both hands radiating along the arm to the chest and neck. On November 26th he dropped dead suddenly; quite unexpectedly.

Autopsy revealed a marked general arteriosclerosis including the cerebral arteries, very marked endarteritis of the small arteries of the kidneys with thrombosis and development of anaemic necrotic infarcts, marked hypertrophy of the left ventricle of the heart with slight dilatation, endarteritis in some of the smaller branches of the coronary arteries and moderate diffuse thickening of the perivascular connective tissue of the myocardium, pulmonary oedema, passive congestion and oedema of the abdominal viscera, healed epididymitis and atrophy of the left testicle, chronic arthritis of right knee. No gross evidence of syphilis was discovered in a very carefully conducted complete autopsy.

This observation appears to be quite unusual in several respects. It is certainly unusual to find such a severe general arteriosclerosis in a patient at the age of 40. The smaller arteries of the kidneys were particularly severely affected and the thrombosis of some of these diseased vessels led to the formation of anaemic necrotic infarcts. The stems of the coronary arteries were nearly normal, but some of their branches also were seriously diseased. The perivascular thickening of the connective tissue in the myocardium suggests an old rheumatic myocarditis. If we are ever justified in speaking of an acute case of arteriosclerosis, this one should be so classified, and the sudden death of the patient, so exceptional without severe myocardial lesions, might be explained by this fact. With it all his blood pressure was not so very high (154–110). There was nothing in the arterial lesions to suggest their syphilitic origin, and on the basis of the statistics quoted above I am rather inclined to believe that his rheumatic infection was of more importance etiologically than his undoubted coexistent syphilitic infection.

III. *Cases with Decompensation, Death from Haemorrhagic Softening of Brain*

(1) (XX-139, 23255, S. F. H.) Man of 50, general arteriosclerosis, little involvement of kidneys, hypertension, hypertrophy and dilatation of the heart, syphilis of cerebral arteries, haemorrhagic softening of brain.

W. S., 50 years, dairyman and teamster; entered March 27, 1917, died April 10, 1917.

Family history unimportant.

Personal history: Patient had the usual infectious diseases of childhood. When 25 years of age he contracted syphilis, which apparently had been very poorly treated, otherwise he denied having had any severe infections. There were absolutely no disturbances until the beginning of his present illness which commenced about three months before entrance, when he noticed dyspnoea on exertion, swelling at ankles extending to knees, which disappeared at night. His abdomen also was swollen at times.

Clinical examination showed dyspnoea, cyanosis, enlargement of heart on both sides, no murmur. The second pulmonic tone was accentuated. The pulse was regular, varying between 80 and 110. The lower extremities and the trunk were markedly oedematous. Dullness and rales were found at the bases of both lungs. A small amount of albumin was discovered in his urine, no casts. The Wassermann reaction in his blood was ++. His temperature was slightly elevated. His blood pressure was 160-110. Under appropriate treatment he improved considerably. On April 9th he suddenly developed a complete paralysis of his left side including face and tongue. He became very noisy, delirious, developed Cheyne-Stokes' respiration and died the next day.

Autopsy revealed marked general arteriosclerosis with marked involvement of renal arteries and their larger branches, little involvement of renal arterioles, few small scars in kidneys, marked hypertrophy and dilatation of heart (2 times normal size) general oedema, cyanotic atrophy of liver, syphilis of the cerebral arteries, large area of haemorrhagic softening in right hemisphere, embolus in branch of pulmonary artery with development of haemorrhagic infarct in lung, healed tuberculosis of lungs, broncho-pneumonia.

(2) (XX-112, L. H. 51018.) Man of 62, chronic tonsillitis with pus in dilated crypts, moderate general arteriosclerosis involving arteries of brain and kidneys, normal blood pressure, but marked hypertrophy and dilatation of heart, recent haemorrhagic infiltration of basilar ganglia of brain on left side, doubtful skin eruption and positive Wassermann reaction.

H. D. C., 62 years, hotel clerk; entered hospital February 6, 1917, died February 19, 1917.

Family history unimportant.

Personal history: Patient had the ordinary infectious diseases of childhood including scarlet fever and diphtheria. At 25 he had a severe attack of typhoid fever. He had had several attacks of tonsillitis and had acute rheumatism in his right hand three or four years ago. Ten years ago a laparotomy was done. At that time his abdomen was swollen, but no other data could be obtained and no reason for the operation was found at autopsy. Otherwise he had always been in excellent health until two years ago when he noticed dyspnoea and palpitation of the heart on exertion. Since then he had to urinate four or five times during the night. One year ago a chronic oedema developed in his left leg. One month before entering the hospital he contracted a severe cold. Coincidentally the palpitation and the dyspnoea increased; an itching papulo-vesicular eruption suddenly appeared on the skin of trunk and extremities. This eruption later became covered with scabs and persisted to the time of his death. A Wassermann test, made shortly before his death, was strongly positive. He had lost 20 lbs. in the last two months before entrance. He used alcohol and tobacco to excess at times.

Clinical examination showed severe dyspnoea and marked cyanosis, very poor teeth, much pyorrhoea, chronic tonsillitis, marked enlargement of the heart, marked oedema of both legs and feet, dullness and moist rales at base of lung, absolute irregularity of pulse rhythm, a pulse rate of 90 at the wrist and a rate of heart beats of 140. For some time every third or fourth heart beat would not come through to the wrist. His blood pressure was constantly about 130-95. He had the usual signs of pulmonary emphysema. His liver was moderately enlarged and tender. Many varicose veins were found in his right leg and the skin over it was deeply pigmented. His sense organs were normal. A light cloud of albumin and a few hyaline and granular casts were found in his urine. His temperature varied irregularly between 99-102° F. He had a slight leucocytosis (14,800). His blood was otherwise normal.

On February 12th he suddenly developed a hemiplegia of the right side and complete aphasia without loss of consciousness. Since then he gradually became stuporous, developed Cheyne-Stokes' respiration and died in coma.

Autopsy revealed very poor condition of few remaining teeth, chronic tonsillitis with concretions and pus in dilated crypts, slight atheroma of aorta, large arteries normal everywhere, moderate arteriosclerosis of the small arteries in kidneys and in spleen, few microscopic scars in kidneys, marked hypertrophy of left ventricle and moderate dilatation of both ventricles (heart about 1½ times normal size), thrombosis in left auricle and in left ventricle, recent embolic anaemic infarct in left kidney, normal arteries at base of brain, small old area of softening on lower surface of right frontal lobe, diffuse haemorrhagic infiltration of left nucleus caudatus, nucleus lentiformis and anterior part of the thalamus opticus, oedema of legs, moderate hydrothorax on right side, old scars at both apices, purulent bronchitis and broncho-pneumonia.

This second case is of particular interest because clinically there were marked symptoms of heart disease, but the blood pressure was constantly low and anatomically the aorta and the large arteries were normal; there was comparatively little in the small arteries and with it all there was a marked hypertrophy and beginning dilatation of the left ventricle.

In both instances the cerebral lesion consisted in a peculiar haemorrhagic infiltration of the brain tissue, different from the ordinary anaemic softening or from an acute arterial haemorrhage.

IV. *Late Cases, Death from Decompensation*

(1) (XXI-32, L. H. 58502.) Man of 70, marked general arteriosclerosis, moderate hypertension, hypertrophy and dilatation of heart, large scars in myocardium, decompensation.

J. D., 70 years, American ranger and cow puncher; entered September 15, 1917, died October 8, 1917.

Family history unimportant.

Personal history: Patient had pneumonia in early childhood and suffered at times from severe frontal headaches with nausea. Otherwise he had always been exceptionally well and strong. There was no history of venereal infection and the Wassermann reaction of his blood was negative. About 2 years before his death he began to have attacks of asthma, eight months later he had a very severe attack associated with much cough, shortness of breath and great weakness. His feet and legs became greatly swollen, so much so that his skin burst over the swollen areas and discharged freely. The raw places on his legs never healed and his dyspnoea became more marked; his cough also continued.

Clinical examination showed great emaciation, slight jaundice, marked emphysema, enlargement of heart, a soft systolic murmur at the apex. His pulse was slow, about 68 per minute, irregular; there were few extrasystoles. The second pulmonic tone was accentuated. The palpable arteries were sclerotic. His blood pressure registered 168-85. He still had marked oedema of his legs with oozing from large raw surfaces in the skin. His temperature occasionally would rise to 100° F. Urinalysis showed a light cloud of albumin, few hyaline casts, few leucocytes. 35 mgms, of urea were found in 100 cc. of blood. During his stay at the hospital the patient improved slightly, for a while, then his condition became worse. He was more or less somnolent. On October 4, 1917, he fell out of bed, bruising his head severely but without injury to the skull. After this he failed rapidly. His pulse continued slow and irregular to the end.

Autopsy revealed marked general arteriosclerosis, slight arteriosclerosis of stems of coronary arteries but marked lesions in the smaller branches with large scars in the myocardium, slight involvement of renal arteries, few small superficial scars in kidneys, marked enlargement of the heart (1½ times normal size), beginning cyanotic atrophy of liver, oedema of legs, emphysema, large old tuberculous scar in upper lobe of left lung with signs of recent recrudescence, terminal broncho-pneumonia.

(2) (XXI-16, L. H. 56091.) Man of 83, marked general arteriosclerosis, moderate hypertension, marked hypertrophy and dilatation of heart, obstructive arteriosclerosis of coronaries and scars in heart muscle, marked involvement of arterioles of kidneys, many small scars in renal cortex, history of "malaria" as a child, and remnants of healed endocarditis of aortic and mitral valves.

F. J. W., 83 years, miner; entered July 3, 1917, died August 29, 1917.

Family history unimportant.

Personal history: Patient had mumps as a child and "malaria" at age of 12. He had always been well, until eight years before entrance to hospital, when he noticed shortness of breath, palpitation of the heart, and when drop beats were first discovered. He also had a dry, non-productive cough. The shortness of breath had become worse during the last 1½ years and the disturbances had been very severe during the last two weeks, when he also noticed swelling of feet.

Clinical examination showed marked cyanosis, marked dyspnoea of Cheyne-Stokes type. He had a slight dry cough. His tonsils were atrophied. There were only two teeth left in his jaws. The thorax was barrel-shaped and there were signs of emphysema. The heart was found moderately enlarged on both sides. A systolic murmur was heard at the apex and in the mitral area. It was faintly audible in the axilla. The pulse-rate was 82, at times faster. Occasionally a beat would not come through to the wrist. His blood pressure was 168-130. There was a slight pitting oedema at both ankles. The superficial arteries were tortuous and very sclerotic.

The amount of urine secreted varied from 280-1160 cc., mostly about 600 cc., the specific gravity between 1019-1025. The urine contained a faint trace of albumin and occasionally a few casts. About 25% of phenolsulphonephthalein was excreted in two hours. On July 23d, 100 cc. of blood contained 69 mgms. of urea. Blood examination showed 72% Hb. and 4,000 000 erythrocytes and 9200 leucocytes. The Wassermann reaction of his blood was negative.

The patient's condition did not change very much during his stay at the hospital. Towards the end of July he became sleepy, stuporous, at times confused. Then he became delirious. The blood pressure decreased to about 145-95. He recovered sufficiently to leave the hospital for a few days. Towards the end signs of pneumonia developed at the bases of the lungs. On August 29th he suddenly collapsed while sitting in a wheel chair and died.

Autopsy revealed marked arteriosclerosis of cerebral arteries but there were no areas of softening or haemorrhage, moderate fibrous thickening of edge of mitral extending to tendinous cords, marked thickening and calcification of aortic valves with moderate stenosis of aortic orifice, very marked arteriosclerosis and calcification of aorta and of all large arteries, very marked arteriosclerosis of small arteries and arterioles in spleen and kidneys, many small subcapsular scars in kidneys, marked hypertrophy and dilatation of heart (2 times normal), marked arteriosclerosis of coronary arteries, scars of moderate size in heart muscle, emphysema, old pleurisy on right side, hydrothorax on left, oedema of legs and scrotum, moderate hypertrophy of prostate, chronic atrophic gastritis and terminal broncho-pneumonia.

(3) (XIX-27, S. F. H. 13468.) Man of 75 years, very marked general arteriosclerosis, hypertrophy and dilatation of heart, severe arteriosclerosis of coronaries with small scars in myocardium, ulcer of duodenum, cardiac decompensation, thrombosis of pelvic veins, haemorrhagic infarcts in lungs.

P. S., 75 years, Italian cook, entered July 10, 1915, died October 4, 1915.

Family history unknown.

Personal history: Patient was a very old man whose memory was evidently impaired. It was therefore impossible to obtain a satisfactory history. All that could be learned was that he had had measles as a child, had had typhoid fever about ten or twelve years ago and later had had ulcers on his left leg. He also stated that he had had to get up at night three or four times to urinate as long as he could remember.

About ten months before he died, he began to suffer from severe dyspnoea, palpitation of the heart and dizziness. He also complained of pain in the left lumbar region, extending down the inner side of his left leg, and of great weakness.

Clinical examination showed dyspnoea, puffiness of skin about the eyes, emphysema with asthmatic breathing, dullness at right base, enlargement of heart on both sides, a rough systolic murmur at apex, slight enlargement of liver, enlargement of prostate, bubonocele. His systolic blood pressure was 110. Patient had a slight fever and a leucocytosis of 13,000 with 83% neutrophilic cells. His urine contained much albumin and some pus but only few casts were found. Patient gradually failed. His dyspnoea increased. His legs became oedematous and he began to expectorate bloody sputum which continued off and on until he died.

Autopsy revealed very marked general arteriosclerosis, hypertrophy and dilatation of the heart on both sides (heart twice normal size), marked arteriosclerosis of coronary arteries with partial obstruction, few small scars in heart muscle, marked arteriosclerosis of branches of renal arteries, many small scars in cortex of kidneys, shallow ulcer of duodenum, cyanotic atrophy of liver, general cyanosis, puffiness of face, oedema of legs and genitals, slight ascites, hydrothorax, thrombosis of pelvic veins, embolism of branches of pulmonary artery with formation of haemorrhagic infarcts in lungs, emphysema, hypertrophy of prostate, cholelithiasis, false diverticulum of duodenum, lipoma in left inguinal region.

(4) (XIX-51, S. F. H. 14646, 15134.) Man of 60, slight lesions in large arteries, very marked endarteritis in small arteries, large scar in left ventricle, anaemic necrotic infarcts in spleen and kidneys, marked hypertrophy and dilatation of heart, extra systoles, anginoid pains, decompensation, slight healed endocarditis.

G. F. M., 60 years, American carpenter; first entered September 30, 1915, died November 13, 1915:

Family history unimportant.

Personal history: Patient had the usual infectious diseases of childhood. He denied ever having had any severe infections. He had three attacks of gonorrhoea, the last one at 56. He had had no syphilitic infection and his blood gave a negative Wassermann reaction. He chewed tobacco and used alcohol moderately. He had had some indefinite heart trouble before, but he noticed the first serious disturbance in January, 1915, when he had a severe cough, precordial pain, shortness of breath, swelling of legs and an enlarged liver. In three weeks, cough, precordial pain, oedema and enlarged liver disappeared, but his dyspnoea persisted. When he came to the hospital in September he showed dyspnoea, slight enlargement of the heart, irregular pulse with many extrasystoles (heart beats 110, pulse at wrist 60 per minute). His systolic blood pressure was 130. His urine and his temperature were normal. On October 14th, he had an attack of severe precordial pain lasting five to six hours. He was discharged improved on October 20, 1915, but returned on November 9, 1915, having been in bed with fever, night-sweats and vomiting in the meantime. For the last five days before coming back to the hospital he had an irregular dull pain on the right side in the region of the liver and a slight jaundice had appeared (cholelithiasis).

Clinical examination at this time showed jaundice, cyanosis, slight dyspnoea, no oedema, pulse very irregular (heart-beats 150, pulse at wrist 116 per minute), dullness at both bases, enlargement of liver, tenderness and rigidity in right upper quadrant of abdomen. (This pain later was referred to the whole hepatic area). The jaundice gradually disappeared. His blood pressure was still at 130. His condition became worse rapidly and he died on November 13, 1915.

Autopsy revealed slight atheroma of aorta, otherwise normal large arteries, endarteritis of small branches of coronary arteries, large scar in anterior wall of left ventricle, marked fairly acute endarteritis of small arteries in spleen and kidneys with formation of multiple anaemic necrotic infarcts in both organs, less involvement of arterioles in kidneys, few small scars in cortex, very marked hypertrophy and dilatation of both ventricles of the heart (heart 2½ times normal size), slight healed endocarditis of mitral and aortic valves, thrombosis of pelvic veins and embolism of branches of the pulmonary artery with formation of haemorrhagic infarcts in lungs, extreme passive congestion of kidneys, many casts in tubules, cyanotic atrophy of liver, marked general cyanosis, no oedema, cholelithiasis, nodular hypertrophy of prostate, lymphangiectases in intestinal submucosa.

(5) (XX-172, S. F. H. 22517.) Man of 41, limited arteriosclerosis, low blood pressure, very marked hypertrophy and dilatation of the heart, very severe precordial pain, death from myocardial insufficiency.

J. H., 41 years, logger; entered February 14, 1917, died June 16, 1917.

Family history unimportant.

Patient did not remember ever having been ill, but has always done the hardest kind of work on railroads, in shipyards and logging. He denied venereal disease and the Wassermann reaction was negative. He was a heavy whisky drinker at times, but used little tobacco. In January, 1915, he had his first attack of dyspnoea, palpitation, dry cough and oedema of the feet. This incapacitated him for five months. He eventually recovered but occasionally still suffered from palpitation and dyspnoea. An exacerbation of his previous symptoms occurred two months ago associated with precordial pain, feverish feeling and much sweating. The pain was very severe day and night and lasted for several weeks. Later he had pains in his left arm similar to those in chest.

Clinical examination showed: cyanosis, dry cough, dyspnoea of Cheyne-Stokes type. His teeth were fairly good, his tonsils small. The veins of the neck exhibited presystolic pulsation. Rales were heard at the bases of the lungs. The heart was distinctly enlarged. A systolic murmur was heard at the apex, which was transmitted to axilla and back. On the right of the sternum there was a to and fro murmur. The second pulmonic tone was accentuated. There were numerous extrasystoles. The blood pressure registered 128-76. The spleen was enlarged and hard. No bacteria were found in the blood on repeated cultivation. There was no oedema. The temperature was irregular, at times above normal. Eight days of high fever were observed at the beginning of May and there was an increase in the leucocytes to 51,000 per cmm. The pulse rate varied very much, fluctuating between 90-120 per minute. The blood was nearly normal (5 million reds and 85% Hbg.). The urine contained a slight trace of albumin, some granular casts, at times some blood. The condition of the patient changed very little while he was at the hospital. At one time he developed slight oedema of the ankles which, however, disappeared again in a short while. Towards the end he had several severe attacks of dyspnoea and cyanosis with feeling of impending death.

Autopsy revealed marked arteriosclerosis of the coronary arteries and moderate lesions in the pulmonary arteries, also some arteriosclerosis of the small arteries in the spleen. The arteries of the kidney and the kidney tissue were normal. The other arteries and the aorta were normal. The heart was very markedly hypertrophied and dilated on both sides (3 x normal size). The heart valves were normal except the aortic cusps, which were very slightly thickened. Some small scars were found in the hypertrophied wall of the left ventricle. The liver showed a beginning cyanotic atrophy. There was a general cyanosis and some oedema of the lower extremities and of the lungs.

(6) (XX-104, S. F. H. 22337.) Man of 80, marked general arteriosclerosis, marked hypertrophy and moderate dilatation of left heart, thrombosis of one of the branches of right coronary artery and large calcified scar in the wall of left ventricle, gout, gastric ulcer, old abscess of prostate.

J. R., 80 years, linotype operator, entered February 3, 1917, died February 7, 1918.

Patient entered in comatose condition so that no history could be obtained.

Clinical examination showed a soft swelling on left side of neck, a heart of normal size. The heart sounds were weak but otherwise normal. Dullness and rales were observed at the bases of both lungs. There was a marked sclerosis of the radial arteries. He had large bed sores and his ankles and knees appeared to be painful. The patient had an irregular temperature going up to 101° F. and his pulse was high and irregular. The Wassermann reaction of his blood was negative. The patient remained delirious all the time and at the end developed Cheyne-Stokes respiration.

Autopsy revealed very marked general arteriosclerosis, with much calcification, marked hypertrophy and moderate dilatation of left ventricle, (heart about 1½ times normal size), slight oedema of ankles, old thrombosis of one of the branches of the right coronary artery and large calcified scar in the wall of left ventricle, very marked arteriosclerosis of small branches of renal arteries including arterioles with many small scars and some of larger size in kidneys, gouty deposits in kidneys and basal joints of great toes, chronic gastric ulcer with marked arteriosclerosis of arteries in base of ulcer, old abscess and beginning carcinoma of prostate, emphysema, chronic purulent bronchitis and broncho-pneumonia, decubitus.

(7) (XXI-109, L. H. 44945.) Man of 48 years, irregular general arteriosclerosis, moderate hypertension, very marked hypertrophy and dilatation of the heart, large scars from healed focal nephritis in the kidneys, healed tonsillitis, death from decompensation.

C. S., 48 years, American rancher; first admission February 5, 1917, died March 9, 1918.

Family history unimportant.

Personal history: When a child patient had measles, mumps and whooping cough and during his boyhood several attacks of tonsillitis. Later he had frequent attacks of stiffness of various joints. As a result of an infected wound on his leg he had "blood poisoning" for some time. At the age of 42 he had "malaria" and he was troubled with it again the following year. When he had "malaria" there was much blood in his urine. For some time he had noticed attacks of palpitation of the heart following severe exertion. For the last six years he had to get up two or three times at night to urinate. He had had gonorrhoea several times but denied infection with syphilis. The Wassermann test was negative both with blood and spinal fluid. He had often used alcohol to excess.

About 1½ years before he died he first noticed dyspnoea on exertion which grew progressively worse, so much so that at times he had to sit up in bed at night.

Clinical examination about a year before his death showed very marked cyanosis and dyspnoea, cough, bad teeth, dullness at both bases, many mucous rales, marked enlargement of the heart, a systolic murmur at the apex, marked irregularity of pulse, many extrasystoles, a blood pressure of 168-112, an enlarged, palpable liver, oedema of legs, moderate sclerosis of palpable arteries. His temperature at first was slightly elevated, later somewhat subnormal. His urine contained a heavy cloud of albumin, no casts, few leucocytes and many red cells. The phenolsulphonephthalein output was 32% in two hours. Under proper treatment he improved rapidly and was discharged February 18, 1917. He returned October 17, 1917, with the same complaint. The clinical findings were similar to those made at the first admission. The most striking finding was again the absolute arythmia of the pulse and the many extrasystoles. He again had a slight oedema and a loud systolic murmur at the apex. His blood pressure was lower than before, registering 130-80. There was still a heavy cloud of albumin in his urine. This time some hyaline and granular casts were discovered. His blood showed a slight anaemia. He had some signs suggestive of bronchopneumonia, but they cleared up and he was discharged on October 30, 1917. He came back to the hospital on December 3, 1917, in a much worse condition with extreme cyanosis and oedema, very rapid heart action, many extrasystoles. His blood pressure then was 130–80. After his heart had quieted down somewhat, his heart beats would vary between 90 and 110 to the minute and his pulse at the wrist between 60 and 100. His output of urine varied with the condition of his heart but the average quantity was about normal. It always contained some albumin. The specific gravity varied between 1010 and 1015. There were many granular and occasionally hyaline casts. His phenolsulphonephthalein excretion had dropped to 23% in two hours. In spite of all efforts his heart continued to fail and he died on March 9, 1918.

Autopsy revealed slight arteriosclerosis of aorta, coronary and cerebral arteries, more marked arteriosclerosis of the radial and abdominal arteries, and very marked arteriosclerosis of the arteries of the neck and lower extremities and the small arteries of the spleen, pancreas, and kidneys; very marked hypertrophy and dilatation of the heart (heart over four times normal size) with much dilatation of the atrio-ventricular openings, very few small scars in the wall of the left ventricle, the musculature of which otherwise was of normal appearence histologically. The small branches of the coronary artery were normal. The lungs were in a marked state of brown induration and the liver showed an advanced cyanotic atrophy. In the kidneys there were many scars from a healed focal nephritis, marked hypertrophy of the remaining kidney tissue. The small arteries in the kidneys were very much thickened. The large veins in the pelvis were filled with thrombi and there was a recent haemorrhagic infarction in the lungs. The tonsils showed signs of an old healed tonsillitis. The skin and mucous membranes were cyanotic and there was a marked general oedema, some ascites and an accumulation of fluid in the right chest, the left pleura being obliterated by old adhesions.

The first three are records of patients with uncomplicated general arteriosclerosis, chronic hypertension and cardiac failure. All these patients were old men in whom this abnormal condition probably had existed for a long time in a relatively good state of compensation. When they finally came to the hospital they were in their terminal stage of decompensation, which no doubt had been preceded by minor disturbances which had not particularly attracted the attention of these rather indolent persons. Cases of this character, probably, are observed much earlier in private practice and the exact symptomatology during compensation and early decompensation will have to be studied there.

All three had myocardial lesions; these were fairly severe in the first two cases. As stated above, it is difficult to tell exactly how important functionally these lesions are. This much is evident, however, that the two patients with marked myocardial lesions complained more definitely of palpitation, their pulse was irregular and there were extrasystoles.

When these patients arrived at the hospital with broken compensation, their systolic blood pressure was not very high (not above 170 mm. mercury in any case). In Case 2 the systolic pressure later receded to 145. In Case 3 it was as low as 110 during the entire period of observation.

The signs of decompensation were the usual ones: dyspnoea, cyanosis, and oedema.

The renal arteries were slightly affected in Case 1, more severely in Cases 2 and 3, but the kidneys were otherwise practically normal. Urine analysis revealed some albumin and few casts. In Case 2 the phenolsulphonephthalein excretion was distinctly slowed, as it usually is during decompensation.

One of the patients died in sudden collapse, the others failed gradually.

In one of them a haemorrhagic infarct developed in the lungs from embolism into the pulmonary artery of a mobilized piece of thrombus from one of the thrombosed pelvic veins.

The whole picture presented by these cases is well known to clinicians and pathologists. I only wish to emphasize here that conditions of this kind may arise without any serious renal injury.

The rest of the cases are not quite so simple. In Case 4 the aorta and the large arteries were practically normal, but the intima of many of the smaller arteries in the heart, spleen, and kidneys was greatly thickened and several of these diseased arterial branches in the spleen and kidneys had been completely occluded by thrombosis, causing the formation of multiple anaemic necrotic infarcts in these organs. A large scar was found in the anterior wall of the left ventricle, probably the result of complete organization of an area of anaemic necrosis.

The functional disturbances were very much like those in the other cases. The patient complained much of precordial pain and there was a marked irregularity of the pulse with extrasystoles. During the period of observation his systolic blood pressure was low (130). The clinical picture was somewhat complicated by an acute attack of cholelithiasis.

In Case 4, although the large arteries were normal, a widely spread obliterative endarteritis was present in the small arteries of various organs. In Case 5, however, even careful microscopic examination of the smaller arteries failed to reveal any marked lesions except in the coronary and pulmonary arteries. The description of these in the original record reads as follows: "The right coronary artery contains several plaques in the intima. The left coronary is almost entirely occluded about 1 cm. from its point of origin. The branches of the pulmonary arteries of both lungs show thickened atheromatous patches." The left ventricle was very much dilated, the muscular wall much hypertrophied, pale, flabby, whereas the wall of the right ventricle was rather more firm in texture. Gross inspection did not reveal any scars in the myocardium, but on microscopic examination a few small scars were discovered. The clinical symptoms were those of a severe cardiac decompensation with very little oedema. In spite of his enormous heart the systolic blood pressure was low (128–76) during the four months while he was at the hospital. He also complained of much precordial pain which at times radiated into his left arm.

In the remaining two cases the question arises how far the lesions of the kidneys which were present contributed to the pathological complex.

In Case 6 these lesions were not very severe, but a certain degree of renal insufficiency is suggested by gouty lesions both in kidneys and in the basal joints of the great toes. Unfortunately, we do not know enough about the origin of these gouty deposits to be able to evaluate this point very accurately.

The involvement of the kidneys is much more definite in Case 7, in which they were small (measuring 10½x5x3 cm.), distinctly granular with a narrow cortex. Microscopic examination revealed very marked local arteriosclerosis, many scars from healed focal nephritis and a definite compensatory hypertrophy of the remaining tubules. The other arteries were irregularly affected; the aorta, coronary arteries and cerebral arteries being practically normal, the radial and abdominal arteries definitely diseased and the arteries of the neck and of the lower extremities very much altered. In spite of the fact that from an anatomical point of view there is no question as to the serious involvement of the kidney tissue, the clinical record of the functional disturbances reads very much like that of an uncomplicated case of cardiovascular disease and resembles the other records of this subdivision rather closely. There is only one essential difference. This man died at the age of 48, whereas the other similar cases lived to be 60 or more. The existence of the renal lesions may have accelerated the appearance of severe clinical symptoms, but there was apparently not enough trouble in the kidneys to give rise to specific renal symptoms.

To my mind cases of this character are very important in showing that there are border-line cases in which there may be a perfectly justifiable discrepancy of opinion between clinician and pathologist.

After all, if we assume, as I believe we have a right to do, that all these processes are the result of similar causes acting upon different tissues, sometimes acting more in one, sometimes more in the other direction, we shall naturally not be so insistent that there should be established a clean line of cleavage between them or anything even approximating it. The extreme cases are easily segregated, but in between there are many the exact position of which it is difficult to define both from a clinical and from an anatomical point of view.

RELATION OF ARTERIOSCLEROSIS TO NEPHRITIS

I. *Cases with Moderately Severe Renal Involvement*

From an anatomical point of view the following four cases belong to this border-line group, although clinically there was definite evidence of renal disturbance.

(1) (XX-111, L. H. 58139, S. F. H. 27763.) Woman of 57, very marked general arteriosclerosis, hypertension, enormous hypertrophy of heart, moderately contracted kidneys, albuminuric retinitis, general oedema, old syphilis of aorta, death from decompensation, history of tonsillitis as a child.

Mrs. E. G., 57 years, French nurse-maid; entered September 4, 1917, died March 18, 1918.

Family history. One brother died of kidney trouble.

Personal history: In early childhood patient had measles, chicken-pox, mumps, and whooping cough, also a very severe attack of tonsillitis. At eight years of age she had typhoid fever. Occasionally she had transient pains in her knees. She had had palpitation of the heart for many years, had choking sensation in her throat after climbing stairs; she also had to get up two or three times at night to urinate. This she had done as long as she could remember. She had been married, had had no children. Her husband died of a destructive ulcer of the face. She denied venereal infection. She did not use any alcohol. For the last two years, before she came to the hospital, she had swelling of the abdomen on and off and she had noticed a marked shortness of breath for three or four years. She first observed oedema of the legs in August, 1917.

Clinical examination on admission showed some difficulty in speech, bad teeth, dyspnoea, cyanosis, oedema of lower lids and of legs, hard, painful lymph-glands on the right side of the neck anteriorly, emphysema, few rales throughout the chest, enlargement of the heart, systolic murmur at apex and in aortic area, a blood pressure of 195-140 mm. mercury, moderate sclerosis of the palpable arteries. Her pulse was absolutely irregular, between 80 and 100 to the minute; there were some extrasystoles. The urine output was normal in quantity. It contained a heavy cloud of albumin, many hyaline, finely granular and few coarsely granular casts, few red cells, many leucocytes; 35% of phenolsulphonephthalein was excreted in two hours. Her blood was normal. The blood contained 42 mgms. of urea in 100 cc.

Under proper treatment the patient improved very much. Her dyspnoea and oedema disappeared; her pulse became regular; her urine contained less albumin and fewer casts. She was discharged as improved on October 8, 1917, and from then on reported regularly at the clinic. By November 12th, her blood pressure had gone up to 280-150. In December her legs began to swell and her face became bloated. She was then sent to the San Francisco Hospital where it was found that she had oedema of face and legs, ascites, large congested tonsils, crypts filled with cheesy material, enlargement of submaxillary glands, pigeon-breast, emphysema, dullness at bases of both lungs, pleural friction rub at base of left lung, enlargement of heart to the left, musical murmur at apex just preceding second sound. The aortic second sound was accentuated. The liver was enlarged and hard. The skin over the back and chest was covered with a papular and pustular eruption. Her blood pressure then registered 200–130. The palpable arteries were hard. The optic discs were oedematous, the retinal arteries small, contracted, tortuous. There were some retinal haemorrhages and white spots about the fovea. The output of urine was diminished. The specific gravity was 1013-1020. It contained much albumin (.3-.4%), granular and hyaline casts, many renal cells, few polymorphonuclear leucocytes, no blood.

It was also discovered that her pupils reacted poorly to light and no leg reflexes could be elicited. X-ray examination revealed a slight dilatation of the arch of the aorta. Her temperature was very irregular, mostly subnormal. Her pulse rate was high and very varying.

Her dyspnoea became worse, her heart became still larger, positive venous pulsation developed and she died of cardiac failure.

Autopsy revealed old syphilitic aortitis with dilatation of the arch, very marked general arteriosclerosis, extreme endarteritis of the small arteries, especially of those in the kidneys including the arterioles, many old scars of moderate size in kidneys, (the kidneys measured 10½ x 5½ x 5 cm., were somewhat granular), diffuse fatty degeneration, necrosis, and desquamation of the epithelium of the convoluted tubules, very marked hypertrophy and dilatation of both sides of the heart (heart about four times normal size), many small scars in the musculature of left ventricle (only moderate involvement of the coronary arteries, no lesions seen in small branches), thrombus in right auricle, brown induration and haemorrhagic infarcts of lungs, cyanotic atrophy of liver, old infarcts in spleen, healed pelveoperitonitis, anasarca, hydrothorax, terminal broncho-pneumonia.

(2) (XXI-14, S. F. H. 25663.) Woman of 35, marked general arteriosclerosis, hypertrophy of heart, marked endarteritis and large scars in kidneys, albuminuric retinitis, scars in heart muscle, areas of softening of brain, healed pelveoperitonitis, healed endocarditis and pericarditis.

Mrs. B., housewife, 35 years; entered August 9, 1917, died August 22, 1917. Patient was transferred to the San Francisco Hospital from the German Hospital in a delirious condition. No history could be obtained. According to her husband her trouble started after a self-induced abortion about eight months ago. Two weeks after this occurrence, which was otherwise uncomplicated, oedema developed and she had to go to bed. The oedema gradually progressed upwards. During the first three months there was marked polyuria followed by almost complete anuria for about four days. She then took some vegetable decoction and polyuria set in again. About one month before entrance she became mentally disturbed, was noisy and violent. At the hospital she had numerous general and partial convulsions and died in coma. On account of the restlessness of the patient no thorough examination could be made. Examination of the fundus of the eyes showed pale discs, arteriosclerosis of the blood vessels and few scattered white spots in retina. Toward the end there were signs of pneumonia and leucocytosis of 32,000 developed. Only one urinalysis was made. Nothing abnormal was found in this one sample.

Autopsy revealed healed endocarditis without functional derangement of valves and healed pericarditis, marked atheroma of the aorta and general arteriosclerosis of apparently recent development, very marked endarteritis of branches of renal artery, large scars in kidney (left kindney measured 9 x 4½ x 3 cm. and the right 11½ x 6 x 3½), marked hypertrophy and dilatation of the heart (1½ normal size), marked arteriosclerosis of coronaries and scars in wall of left ventricle, thrombosis of right auricle and of left ventricle near apex, old infarcts of spleen, recent areas of softening in cerebellum and right occipital lobe, slight internal haemorrhagic pachymeningitis, general oedema, ascites and hydrothorax, chronic pelveoperitonitis with closure of Fallopian tubes, cholelithiasis, acute cystitis, and pyelitis, broncho-pneumonia and gangrene of lungs.

(3) (XXI-6, L. H. 46577.) Woman of 44, general arteriosclerosis involving especially cerebral and renal arteries, hypertrophy of heart, large old scars in kidneys, albuminuric retinitis, recent haemorrhages into brain, history of tonsillitis and rheumatism.

Mrs. L. B., 44 years, housewife and waitress; first seen September 26, 1916, died August 4, 1917.

Family history: Mother died at age of 59 from dropsy.

Personal history: Patient had the ordinary diseases of childhood including smallpox and possibly scarlet fever. At the age of 19 she had a severe attack of typhoid fever, later she suffered from "malaria," and also from sore throat and rheumatism. Complete hysterectomy was done in 1913 for "a cluster of tumors." Patient had had to urinate at night, usually once, since childhood. She had had severe headaches associated with vomiting once or twice a month for the last fifteen years. The vomiting had increased in the last three or four years. For the last year she had been vomiting almost daily. She had suffered much from constipation. She had noticed shortness of breath on exercise and occasionally swelling of legs. She had been subject to colds with severe bronchitis. Her eyesight had been becoming less acute for the last two years.

Clinical examination showed moderate conjunctivitis, puffiness of face, moderate pyorrhoea, some enlargement of tonsils, slight oedema of legs; nothing abnormal was found in chest and abdomen. Her urine, in September, 1916, contained a slight trace of albumin and a few hyaline casts; in January, 1917, there was more albumin, many hyaline, granular, few epithelial casts and considerable blood; later the amount of albumin decreased again and no casts were seen. The specific gravity varied between 1010 and 1020. From the beginning she had a definite anaemia (69% Hb.). There was no history of syphilis, but a positive Wassermann reaction was obtained with her blood. She was given antisyphilitic treatment without much benefit. In June, 1917, the Wassermann reaction was negative. In July, 1917, it was discovered that she had a marked albuminuric retinitis. For a while she was treated in the outpatient department. On August 4th she was brought to the hospital with signs of an apoplexy with right-sided hemiplegia. At that time she showed some puffiness of the face, had a systolic blood pressure of 240 mm. mercury, and a large amount of albumin in the urine, but no formed elements except some erythrocytes. She died without regaining consciousness.

Autopsy revealed a marked general arteriosclerosis which was especially marked in the arteries of the brain and of the kidneys. In the kidneys the small arteries were involved especially. The left kidney was fairly normal, measuring 12 x 6 x 3½ cm., but in the right one there were large scars and its size was reduced to 9 x 4½ x 2¼ cm. The heart was distinctly enlarged (about 1½ times normal size) and the wall of the left ventricle was very thick, averaging 15 mm. in diameter. The coronary arteries were normal. The heart muscle showed some small areas of fatty degeneration. In the left internal capsule there was a recent haemorrhage about 1½ cm. in diameter and another large recent haemorrhage was found in the right hemisphere of the cerebellum. There was some oedema of face and legs.

(4) (XX-10, L. H. 44330.) Man of 38, moderate general arteriosclerosis with severe disease of arteries of kidneys and renal scars of moderate size, marked chronic hypertension and cardiac hypertrophy and dilatation, terminal exacerbation of process in kidneys (acute endarteritis of arterioles and acute glomerulonephritis). Pus pockets in tonsils and history of "malaria." Slight healed endocarditis. Death in uraemia.

A. Y. T., 38 years, farmer; entered hospital July 26, 1916, died August 18, 1916.

Family history: Father and one brother are said to have had Bright's disease.

Personal history: Patient had ordinary infectious diseases of childhood but no severe infections except an attack of "malaria" at age of 31 which lasted three months. He has had a chronic unproductive cough for eight to ten years and occasionally fluttering of the heart for several years, also distension of abdomen with colicky pains, but no dyspnoea or any other serious symptoms until one year before his death when he commenced to have attacks of dizziness, dyspnoea, palpitation and dry cough. These attacks had become more frequent and more severe. During the last year he had been feverish occasionally and had had night sweats. Recently he noticed that his urinary output was decreasing. He had nocturia occasionally. He never noticed any polyuria. Four days before admission he noticed oedema of the legs for the first time. Patient had lost fifty pounds in weight.

Clinical examination revealed extreme dyspnoea, cyanosis of the skin, oedema of legs and genitals, marked enlargement of the heart, loud blowing systolic murmur at apex transmitted to axilla and back, enlargement and tenderness of liver. The second pulmonic sound was accentuated. The fingers were clubbed and cyanotic. The blood pressure was steadily about 210-140. The pulse varied between 80-120, was distinctly irregular in rhythm. The temperature curve was quite irregular between 96-100° F. The tonsils were moderately enlarged and the crypts contained some pus. The average amount of urine secreted was about 500 cc. daily. It contained much albumin, many hyaline, granular epithelial and few blood casts, few leucocytes and some red blood corpuscles. The amount of blood present varied in different specimens. About 30% of phenolsulphonephthalein was secreted in two hours. Seven days before his death the urea content of blood was 172 mgm. in cc. There was no Wassermann reaction and a blood culture gave a negative result. The haemoglobin was estimated at 95%. There was a definite increase in the number of leucocytes which gradually rose from 12,600 to 25,000 in cmm. with a preponderance of neutrophilic cells. Patient complained that lately he frequently had specks before his eyes but his backgrounds were normal.

While he was at the hospital the oedema subsided somewhat. He had a severe attack of abdominal pain radiating through the back. The patient became progressively weaker, more uncomfortable. Cheyne-Stokes type of respiration developed and continued for several days. There was some vomiting. In the end the patient became comatose with periods of restlessness, and apparently visual hallucinations. He died in coma.

The following lesions were found at autopsy: slight rather recent atheroma of aorta with round-celled infiltration in media, moderate old arteriosclerosis of medium-sized arteries, very marked old arteriosclerosis of small branches of renal arteries, acute severe endarteritis of arterioles, polymorphonuclear leucocytes in some glomeruli, and blood, leucocytes and casts in some tubules, moderate number of old fibrous glomeruli surrounded by old scars of moderate size (kidneys in gross granular but not shrunken), only slight degenerative lesions in the epithelial cells of the comparatively many normal tubules, marked hypertrophy and dilatation of the heart (twice normal size), old moderate cyanotic atrophy of liver, chronic tonsillitis, slight healed endocarditis, oedema of lower extremities and of genitalia, terminal broncho-pneumonia and pleurisy due to streptococcus infection.

These cases are particularly interesting because they demonstrate that comparatively limited lesions in the kidney may be associated with functional disturbances which we usually ascribe to renal insufficiency.

Three of these four patients died at an early age (between 35 and 45).

There was either a history of tonsillitis or other signs of an old septic infection.

Nocturia was a constant symptom. The urinary findings were very definite, at least at certain times during the course of the disease. The phenolsulphonephthalein excretion was distinctly lowered in the two cases in which it was determined. The systolic blood pressure was high, much higher than in the uncomplicated arteriosclerotic cases, ranging above 200 and in Case 1 at one time running up to 280.

Facial oedema was observed commonly and, what is most remarkable, three of the four patients had an albuminuric retinitis.

Patient 2 had numerous convulsions and Patient 3 suffered from headache and vomiting.

Patient 3 also had a marked anaemia. In the others the haemoglobin percentage was normal.

Death occurred from cardiac failure in the first case, from softening of the brain and severe broncho-pneumonia in the second, from apoplexy in the third, and from uraemia with high blood urea in the fourth. This death in uraemia, however, was evidently due to the fact that the patient developed an acute diffuse glomerulonephritis in addition to the comparatively slight old lesions which existed in his kidneys.

Autopsy in all four patients revealed a marked general arteriosclerosis (somewhat less far advanced in Case 4 than in the others), marked hypertrophy and dilatation of the heart, and definite, although limited, chronic lesions in the kidneys.

II. *Chronic Cases with Severe Renal Involvement*

It is of some interest to compare with these cases the records of those in which a severe chronic nephritis was present in addition to the general arteriosclerosis.

(1) (XX-38, 19392 S. F. H.) Man of 32, chronic tonsillitis with old pus pocket in one tonsil, old glomerulonephritis with very marked local and general arteriosclerosis, concentric hypertrophy of left ventricle, albuminuric retinitis, death in uraemia.

N. E., 32 years, Italian, boiler maker; entered August 11, 1916, died October 7, 1916.

Patient had "malaria" at the age of 15. About 1½ years ago he had a bad cough and six months later he noticed oedema of the feet, also of face and abdomen, persisting for about seven months. He was treated at the hospital and left very much improved. For the past months his face had been swollen in the morning and his feet would swell when he got up. He had suffered much from headache and he had to get up four or five times at night to urinate. He did not complain of dyspnoea. Four months ago he became blind, but he gradually recovered his eye-sight in two months. He constantly had a bad cough with more or less bloody sputum. Occasionally he observed spasms in his left middle-finger. He denied venereal infection. He took very little alcohol, but was a heavy smoker.

Clinical examination showed a very severe anaemia, small sclerosed tonsils "without active focus" (careful examination by specialist), impaired resonance at bases of lungs, a heart within normal limits, a systolic murmur over mitral area, slight oedema of legs. The systolic blood pressure was 205; it later decreased to 160. Examination of the backgrounds of the eyes revealed bilateral neuro-retinitis with many fine haemorrhages. The amount of urine excreted varied between 1000 and 2500 cc. It contained much albumin, many hyaline, granular and fatty casts, at times blood corpuscles, few leucocytes. Only a trace of phenolsulphonephthalein was excreted in two hours. The pulse varied between 80 and 100. The temperature curve was quite irregular, between 98 and 101° F.

While at the hospital the patient suffered much from severe headache; he had frequent nosebleed. On September 25th symptoms appeared of acute tonsillitis. The tonsils were enlarged and covered with gray spots. There was also some enlargement of the lymph glands of the neck. Two days later a tooth abscess developed which was opened the following day. On account of the severe anaemia, the haemoglobin having decreased to 20%, a transfusion was done on September 29th, which brought up his haemoglobin to 45%. In spite of this the patient became comatose, developed muscular twitchings and died, evidently in uraemia.

Autopsy revealed severe chronic glomerulonephritis with marked shrinkage and almost complete destruction of the renal cortex, very marked endarteritis of smaller and larger branches of renal arteries, marked general arteriosclerosis with moderate involvement of aorta and coronaries, marked concentric hypertrophy of left ventricle (heart 1½ x normal size), oedema of cheeks, slight icterus, pigmentation of skin of lower abdomen and lower extremities, furunculosis, acute conjunctivitis, inflammatory swelling of left cheek and neck from abscess of tooth. The right tonsil was small, heavily scarred. Deep in the center of the left tonsil there was an old pus pocket. The upper pole of the left tonsil was acutely inflamed and partly necrotic.

(2) (XIX-13, L. H. 4510.) Man of 39 years, severe chronic glomerulonephritis with extreme endarteritis in kidneys, marked general arteriosclerosis, hypertension, hypertrophy of left ventricle, uraemia, pulmonary oedema, history of tonsillitis.

H. S., 39 years, Japanese laborer; first entrance January, 1915, died August 31, 1915.

Family history unimportant.

Personal history: Patient had had measles as a child, a severe attack of typhoid when 16. He never had had rheumatic fever, but he had had sore throat occasionally. He continued in good health except for occasional palpitation and some precordial pain until eight months before his death, when he had another attack of sore throat followed shortly by the development of anasarca. At that time he recovered in a few days. Six months later the general oedema recurred accompanied this time by nausea, headache and general weakness. He also complained that his vision had become dimmed. At this time he also had polyuria; his urine was pale, of low specific gravity. It contained much albumin, many epithelial, blood, granular and hyaline casts, also free blood. His blood urea concentration was 0.276%. He had to get up three or four times at night to urinate.

Clinical examination, two weeks before his death, showed marked weakness and emaciation, poor teeth, large ragged tonsils, dullness, many coarse and fine rales at left apex, slight dullness and fine rales over bases of both lungs, marked enlargement of heart, a rough systolic murmur at the apex and a harsh to and fro murmur over the sternum at the level of the third rib. His pulse was rapid, regular, of good volume. His blood pressure was 225-125. His skin was very dry, atrophic and loose. There was no oedema. His temperature was slightly subnormal. The amount of urine secreted now was low, about 600 cc. and getting less. It was still of low specific gravity. The microscopical and chemical findings were the same as before except that there was less blood in the sediment. He had a severe anaemia (2½ million red blood corpuscles and 50% haemoglobin). No phenolsulphonephthalein was eliminated in 3½ hours. The urea concentration of his blood went up to 0.510% and his blood pressure rose very high. He vomited much, passed gradually into uremic coma with muscular twitchings and general convulsions. At the time of death the urea contents of his blood was 0.763%.

Autopsy revealed atrophic tonsils, chronic glomerulonephritis with much shrinkage and very extensive destruction of renal cortex, extreme endarteritis in small and larger branches of the renal arteries, marked general arteriosclerosis with atheroma of aorta, marked hypertrophy of left ventricle (heart 2 x normal), oedema of lungs.

(3) (XX-32, S. F. 19750, L. 42961.) Man of 42, with chronic nephritis, hypertension and hypertrophy of heart, marked local and general arteriosclerosis, pus pockets in tonsils, fatal cerebral haemorrhage.

L. B., 42 years old, Italian laborer; entered June 21, 1916, died September 29, 1916.

Family history unimportant.

Personal history: Patient had "malaria" for 18 months, 20 years ago. For the last three or four years he had had to get up two or three times at night to urinate. Otherwise he had been quite well, until about 1½ months ago. He was moderate in his habits and denied venereal infection. During the last month and a half he had headache, stomach trouble and had lost about 22 pounds in weight. He vomited several times. He was also short of breath and complained of palpitation of the heart.

Clinical examination showed anaemia, apparently normal tonsils, exaggerated pulsation of carotid arteries, arteriosclerosis of radial arteries, some moist rales at right basis, enlargement of heart, no murmurs, increased blood pressure. (238 systolic which later decreased to 185-135). The urine showed a low specific gravity (1011 or less), contained much albumin, many granular, hyaline, waxy casts, many leucocytes and some red blood corpuscles. There was practically no excretion of phenolsulphonephthalein. There were 2,820,000 erythrocytes in the cmm. of blood. The haemoglobin content of the blood averaged 50%. The white blood corpuscles were normal. The Wassermann test was negative. There was no free HCl in the gastric juice. His temperature was normal; pulse rate 80-100. He continued to suffer from much headache, vomiting, bloody diarrhoea and nosebleed. On September 29th patient had an apoplectic seizure. He became unconscious, his breathing was stertorous, he had spasms in his right arm and leg. His left side was paralyzed; his left eye was partly open and the left corner of his mouth drooped. He died in the attack. The patient had no oedema at any time.

Autopsy revealed chronic tonsillitis with large pus pockets, sphenoidal and ethmoidal sinusitis, severe chronic glomerulonephritis with much shrinkage, very marked endarteritis in arterioles, very marked arteriosclerosis of larger branches of renal artery, marked general arteriosclerosis including cerebral and pulmonary arteries (many areas of round-celled infiltration in adventitia of all arteries and in media of aorta), slight endarteritis and marked endophlebitis of vasa vasorum, marked hypertrophy and dilatation of the heart (2 x normal), beginning cyanotic atrophy of liver, large haemorrhage in right hemisphere under motor region of cortex with perforation into right ventricle, slight oedema of scalp, hydrothorax, hydro-pericardium, pulmonary oedema and broncho-pneumonia.

(4) (XIX-53, L. H. 5069.) Man of 48, severe chronic nephritis with extreme endarteritis in kidneys, marked general arteriosclerosis, hypertrophy of heart, uraemia, history of severe throat infection as a child and healed endocarditis.

G. D., 48 years, American rancher; entered November 13, 1915, died November 19, 1915.

Family history: Father was a hard drinker and died of dropsy.

Personal history: As a child the patient had had a very severe infection of his throat, which was diagnosed as diphtheria. At the age of 25 he had typhoid fever, and pneumonia when 36 years old. He had measles late, at the age of 40. For the last 20 years he had suffered with terrific headaches, accompanied by vomiting and pain in the back of his neck. These attacks lasted for about 24 hours and during them he would sometimes lose his mind. About four years before his death he began to get up about four or five times at night to urinate and a little later his hands and feet began to swell after a hard day's work. The headaches became more constant, but somewhat less severe. For the last three years his eyesight had been failing, becoming quite bad lately. He vomited a good deal and became very weak. He had many nosebleeds and lost about 20 pounds in weight. He came to the hospital about a week before his death.

At that time he was cyanotic and oedematous and there was clinical evidence of a moderate hypertrophy of his heart. His urine was of low specific gravity (1010) clear, acid, contained much albumin, some pus, many epithelial cells. Hyaline, granular and some waxy casts were found in the sediment. His blood urea was high (0.51%) and at autopsy the blood contained even 0.68%. His blood pressure was 230 systolic. His temperature was subnormal. His pulse was regular, between 90-100. During the last days of his life patient was very restless, at times delirious, showed muscular twitchings and had attacks of air hunger.

Autopsy revealed healed endocarditis of aortic valves with no functional disturbance, very severe chronic nephritis with shrinkage and very extensive destruction of renal cortex, extreme endarteritis in all vessels of the kidneys, marked general arteriosclerosis with comparatively slight involvement of aorta, marked hypertrophy of the heart, especially of the left side (2 x normal size), brown induration of lungs, gouty deposits in kidneys, cyanosis, slight oedema of legs and moderate ascites, acute terminal pancreatitis.

These four observations are so characteristic and so similar to each other that they read like selected cases. Still they are the only four cases of this type which we observed in our series. The etiology seems to be clear in all four; the history of the development of the functional disturbances is very suggestive in all; the urinary findings were very well marked; the phenolsulphonephthalein excretion practically nihil, the blood pressure high; headache, nausea, and vomiting common. Three of these patients died in uraemia, one from cerebral haemorrhage. In all of them there was present a marked endarteritis in the kidneys and a marked general arteriosclerosis.

These are the cases which are often described as severe arteriosclerotic nephritis, as if the nephritis were the result of the arterial lesions in the kidneys. This is certainly not so, and our point of view will never be satisfactory until this is thoroughly recognized.

In addition to these four observations, there are two exceptional cases; one in which, in spite of a severe diffuse nephritis and extensive arteriosclerosis, the usual circulatory disturbances were entirely absent, and the other in which contraction of the kidneys arose on the basis of chronic parenchymatous nephritis in amyloid disease.

(1) (XXI-101, S. F. H. 14230.) Man of 60 years, chronic diffuse nephritis, general arteriosclerosis, no hypertension, normal heart, uraemia, advanced chronic pulmonary tuberculosis.

R. W., 60 years, Irish laborer; entered August 28, 1915, died February 24, 1918.

Family history unimportant.

Personal history: He had gonorrhoea for three or four months at the age of 28. Otherwise he had no serious illness except "malaria" when he was 40. He had had to get up twice at night to urinate for the last seven or eight years. He used alcohol and tobacco freely. In March, 1915, he noticed the first symptoms of his pulmonary trouble and in August he was told that he had pulmonary tuberculosis. When he came to the hospital, he had the usual signs of this disease with a moderate involvement on both sides. His circulatory apparatus appeared to be normal. His blood pressure was 124-80. His urine, however, even then contained a faint trace of albumin, few leucocytes and many hyaline casts. The disease in his lungs progressed rather slowly and his condition remained satisfactory until February 1918, when he suddenly developed signs of renal insufficiency. He vomited very frequently, gradually went into coma, showed twitchings and irregular movements of his muscles. The urinary output was much reduced; the urine contained much albumin, many hyaline, granular and fatty casts. No phenolsulphonephthalein was excreted in two hours. The retinal vessels were much distended and the optic discs were markedly choked. His cerebrospinal fluid was normal. He died in uraemic coma.

Autopsy revealed advanced chronic pulmonary tuberculosis and chronic intestinal tuberculosis, marked atheroma of the aorta and marked general arteriosclerosis, normal heart, marked chronic diffuse nephritis with very extensive destruction of renal tissue, extreme local endarteritis in kidneys, oedema of brain, healed pericarditis, cholelithiasis, terminal broncho-pneumonia.

(2) This patient was a male leper, 40 years of age, who died of broncho-pneumonia after having been at the leprosorium for several years. Unfortunately, there was no clinical record. Autopsy revealed general amyloid disease, chronic parenchymatous nephritis with extreme contraction, marked general arteriosclerosis, marked concentric hypertrophy of the left ventricle.

This last case again demonstrates that chronic parenchymatous nephritis in amyloid disease may eventually lead to the development of contracted kidneys with hypertension and general arteriosclerosis, although this certainly must be looked upon as an exceptional occurrence.

In my previous publications emphasis has been placed upon the occurrence of chronic nephritis with hypertension, but without general arteriosclerosis. I have again observed several cases of this kind, showing that these two conditions are by no means directly dependent upon each other.

(1) (XIX-56, S. F. H. 15178.) Man of 26, very severe chronic diffuse nephritis with purely local endarteritis, moderate hypertrophy of heart, chronic osteomyelitis.

F. B., 26 years, Italian teamster; entered November 11, 1915; died November 25, 1915.

Imperfect record: Patient did not remember ever having had any disease. His present complaint commenced with spitting of blood about 1½ months before he died. He also complained of weakness, dyspnoea, cough and night sweats. Since then he had had several haemorrhages from the lungs, but he had little sputum. He had observed no disturbances in urination.

Clinical examination revealed some dullness in the region of the right apex, many fine rales all over both lungs, some bronchial breathing in places. Nothing abnormal was found in throat, heart and abdomen. There are no records of laboratory tests.

Autopsy revealed chronic osteomyelitis of scaphoid bone of left foot, very marked chronic diffuse glomerulonephritis with almost complete destruction of cortex, very marked endarteritis in kidneys, little arteriosclerosis elsewhere, hypertrophy of heart (1½ x normal), broncho-pneumonia.

(2) (XIX-67, L. H. 28140.) Woman of 32, severe chronic diffuse nephritis with extreme endarteritis in kidneys, little elsewhere, hypertension, hypertrophy of heart, slight healed myocarditis, old haemorrhage of brain, albuminuric retinitis, terminal oedema, uraemia, history of chronic tonsillitis.

Mrs. A. McC., 32 years, American housewife; entered May 17, 1915, died December 17, 1915.

Family history unimportant.

Personal history: Patient had the ordinary infections of childhood, including scarlet fever. She also had mild attacks of sore throat occasionally and once in a while headaches which usually did not last more than one day at a time. Otherwise nothing suggestive could be found in her past history. She married at 26, had never been pregnant. She denied venereal infection and claimed that her habits were good. She did not have to get up at night to urinate. Seven months before her death she suddenly lost control of her right leg, then of her right hand and then lost consciousness.

Clinical examination revealed a right-sided flaccid paralysis with diminished sensibility over right side of body and inability to speak. Her blood pressure at that time was high (220-165). Her pulse was rapid. Her heart was apparently normal. Her urine contained a large amount of albumin and a moderate number of granular casts. At times no casts could be found. The amount secreted at first was nearly 1000 cc. in 24 hours, but it later diminished to 500 cc. and less. Her phenolsulphonephthalein output was less than 10% in the first and about the same amount in the second hour; later this also was much more diminished. Examination with the ophthalmoscope revealed swollen discs and haemorrhages and white spots in fovea. Her spinal fluid was under high pressure but otherwise normal. The Wassermann reaction was negative. Her temperature at first was normal, later subnormal and her pulse rate remained high and varying. The examination of her blood did not reveal anything abnormal. During her stay at the hospital her speech gradually improved somewhat and she regained partial control over her right arm and leg, but otherwise she became worse. She had headaches often; she complained much of nausea and vomited frequently. Her blood pressure remained high, the systolic pressure continuing above 200 mm. mercury. She became more and more dyspnoeic, at times her respiration assumed the Cheyne-Stokes type. She also developed oedema of her face and extremities. In the end she was extremely dyspnoeic and became comatose. A few days before her death she had a profuse haemorrhage of bright blood from her rectum.

The autopsy revealed chronic healed tonsillitis, old diffuse nephritis with shrinkage and very extensive destruction of renal tissue, many small remnants of cortex with compensatory hypertrophy, extreme old endarteritis of large and small blood vessels in kidneys, few yellow spots and small plaques in aorta, little arteriosclerosis elsewhere except in splenic artery which was markedly diseased (large arteries of brain free), marked hypertrophy and dilatation of the heart (heart twice normal size), slight subacute myocarditis, old haemorrhagic cyst in region of left Sylvian fissure, cyanotic atrophy of liver, marked general oedema, ascites and hydrothorax, hypostatic pneumonia, pseudo-membranous colitis, chronic cystic mastitis.

(3) This was the most interesting case of all and has already been briefly mentioned above (page 41). The patient, a man of 50, had suffered from symptoms of Bright's disease ever since he was a child. The development of his functional disturbances progressed in the usual manner. He had a high blood pressure constantly, the pathological changes in his urine were well marked at all times. He finally died in uraemia.

Autopsy revealed a very marked old diffuse nephritis with very extensive destruction of the renal cortex, very marked endarteritis in the larger branches of the renal arteries, little in the arterioles of the kidneys. There were a few fibrous plaques in the aorta and a few yellow spots in the intima of his coronary arteries. Otherwise his arteries were absolutely normal. He had a marked concentric hypertrophy of the left ventricle.

If long-continued hypertension alone could cause arteriosclerosis, it certainly should have done so in this case; yet his arteries were perfectly normal, with the slight exceptions mentioned.

III. *Subacute Nephritis and Arteriosclerosis*

The true interrelation of chronic septic infection, nephritis and arteriosclerosis, with their associated functional disturbances, is even more clearly brought out by the cases of subacute nephritis in our series. The following records of such cases are arranged according to the severity of the arterial lesions.

(1) (XXI-42, L. H. 59817.) Boy of 12, chronic suppurative tonsillitis, late subacute nephritis with moderate hypertension and moderate hypertrophy and dilatation of left ventricle, slight lesions in arteries, uraemia.

C. S., Boy, 12 years; entered October 30, 1917, died November 8, 1917.

Family history unimportant.

Personal history: When three years old patient had measles and scarlet fever. After this he was apparently quite well until the age of nine, when blood was discovered in his urine. He had no oedema at that time and his health otherwise remained good. Four months before he died he had a severe attack of enteritis with much pain in the bowels and vomiting which lasted for several months, after which the child never entirely recovered. Frequent colds followed the intestinal disturbances but no history of tonsillitis could be elicited. During the last three weeks before entrance to the hospital his mother noticed swelling of his face, body and feet.

Clinical examination showed drowsiness, dyspnoea, marked pallor of face and of mucous membranes, oedema of face, slight enlargement of tonsils with swelling of the left submaxillary glands. His heart was within normal limits. His blood pressure measured 140-110. His pulse varied between 80 and 140 to the minute; it was regular. His temperature curve was quite irregular, running from 98 to 101° F., at one time. The backgrounds of his eyes were normal. The amount of urine secreted was below normal (between 700 and 800 cc. in 24 hours). Its specific gravity was fairly low (1014–1018). It contained much albumin (about .8%), many granular and epithelial casts, also some hyaline and few waxy casts, many leucocytes, few blood casts and few red blood corpuscles. The elimination of phenolsulphonephthalein amounted to 10% in the first hour and 7% in the second. 102 mgms. of urea were found in 100 cc. of blood.

The child was very uneasy and restless. Towards the end he became somewhat delirious, and signs developed of pulmonary oedema.

Autopsy revealed chronic suppurative tonsillitis, late subacute diffuse glomerulonephritis (large mottled kidneys with numerous punctiform haemorrhages), slight endarteritis in few arteries in the kidneys, more marked lesions in the small arteries of the spleen, few yellow spots in the aorta, otherwise normal arteries, moderate hypertrophy and dilatation of the left ventricle, signs of chronic passive congestion of the lungs and terminal broncho-pneumonia.

(2) (XIX-73, L. H. 34289.) Man of 43, chronic suppurative tonsillitis, marked diffuse subacute glomerulonephritis with moderate endarteritis in branches of renal arteries, other arteries normal, moderate hypertension, moderate concentric hypertrophy of left ventricle, general oedema, uraemia.

P. G., 34 years, Italian rubber worker; entered October 25, 1915, died December 29, 1915.

Family history unimportant.

Personal history: Patient did not remember ever having had any of the infectious diseases of childhood, nor ever having had any severe infections. He had sore throat occasionally, but not very severely, until three months ago when he had a severe tonsillitis. As long as he could remember he had had to get up once or twice at night to urinate. He had gonorrhoea four or five years ago, denied syphilitic infection, but his blood showed a positive Wassermann reaction (syphilitic scar in liver found at autopsy). He drank very large quantities of wine and beer. He first noticed oedema of feet and then of hands, three weeks before coming to the hospital. He developed a marked dyspnoea and when exercising he had some palpitation of the heart. He also complained of frontal headache.

Clinical examination showed marked anasarca, marked enlargement of the tonsils with many pus pockets, fluid in chest, heart of normal size, second sounds loud and ringing, a blood pressure of 170-100, enlargement of liver, fluid in abdomen, normal backgrounds. His pulse was regular, varied between 70 and 90. His urine was of low specific gravity, contained a large amount of albumin, very many hyaline, granular, cellular and blood casts, at times much free blood, many leucocytes. The total quantity was distinctly diminished and did not materially increase when large amounts of water were given. His phenolsulphonephthalein elimination at first was 25% in two hours, but this went down later to 17½% and in the end to 5%. At first his blood was normal, but he soon developed a severe secondary anaemia, the haemoglobin percentage going down to 42 eventually. Several blood cultures had a negative result. During the first two weeks at the hospital he had a marked exacerbation of his tonsillitis which later subsided, when tonsillectomy was performed. Under energetic treatment the anasarca disappeared, but the puffiness of the face remained and the blood pressure and the urinary findings were unaltered. He was discharged very little improved at the end of November, but returned in the middle of December in a bad condition with marked general oedema. He was very apathetic, his tongue was heavily coated. His heart now was distinctly enlarged to the left. His systolic blood pressure remained 160. His liver was very much swollen and tender. The urea contents of his blood was high. The patient became more and more apathetic, showed restlessness, twitching of facial muscles. Signs of pulmonary oedema developed. In the end his respiration was very deep and labored. He died in coma.

Autopsy revealed marked diffuse subacute glomerulonephritis (large mottled kidneys), marked endarteritis in kidneys, normal arteries, slight concentric hypertrophy of left ventricle, thrombosis of right auricle, marked cyanotic atrophy of liver, general anasarca, ascites, hydrothorax, oedema of lungs, old syphilitic scar in liver.

(3) (XIX-116, S. F. H. 14575, 15236.) Woman of 29, Caesarian section and hysterectomy six years ago, followed by infection, obliteration of left ureter and destruction of left kidney, late subacute glomerulonephritis of right kidney with local endarteritis, hypertension, concentric hypertrophy of left ventricle, general oedema, uraemia.

M. F., 29 years, negro dancer; first admission September, 1915, died March 9, 1916.

Family history not obtained.

Personal history: Patient had always been well, until she was 23 years old, when she was confined by Caesarian section and her uterus was removed. Following this operation a large ventral hernia developed. For this she was operated on September 28, 1915, successfully. At that time it was noticed that the second aortic sound was accentuated and that her urine contained a considerable amount of albumin, but no casts were found in two examinations. She returned to the hospital on November 11, 1915, complaining of headaches, dyspnoea, cough, oedema at ankles. She also had signs of pulmonary oedema.

Clinical examination revealed a slight systolic murmur at the apex, systolic blood pressure of 160, an enlargement of her liver. Her temperature varied irregularly between 99° and 102° F., her pulse between 90-110. Her blood gave a negative Wassermann reaction. She left the hospital slightly improved on December 27, 1915, but returned on February 8, 1916, with general anasarca, slight systolic murmur, rales all over the chest, enlargement of liver. Her systolic blood pressure had risen to 200 and more. Her urine now, in addition to the albumin, contained many hyaline and granular casts. She gradually became comatose and died in uraemic coma.

Autopsy showed extensive adhesions in peritoneal cavity from Caesarian section and supravaginal hysterectomy, remnants of old abscesses in adhesions, left ureter surrounded by scar tissue and completely obstructed, left kidney totally destroyed, late subacute diffuse glomerulonephritis of right kidney with marked endarteritis, moderate atheroma of aorta. The other arteries were apparently normal. The left ventricle of the heart showed a marked concentric hypertrophy (heart about 1½ times normal size). The other findings were an extreme general anasarca, ascites, hydrothorax, oedema of lungs and a terminal broncho-pneumonia with incipient pleurisy.

(4) (XX-50, L. H. 44478, S. F. H. 19704.) Man of 52 years, pus pockets in tonsils, late subacute glomerulonephritis with beginning contraction, moderate involvement of arteries of kidneys, recent slight arteriosclerosis in other arteries, progressively increasing hypertension, concentric hypertrophy of left ventricle, uraemia.

C. D. G., 52 years, cook; entered hospital July 29, 1916, died November 1, 1916.

Family history unimportant.

Personal history: Patient had the ordinary infectious diseases of childhood. Fifteen or twenty years ago he had had many attacks of sore throat, since then the attacks had occurred more rarely. Otherwise he was strong and perfectly well, until about fifteen months before his death when he had rheumatism in knees, ankles and hip and shooting pains in region of heart. This condition lasted about three months. He did not stay in bed, but was incapacitated for work. About the same time he noticed that he voided an unusually large amount of urine. Later there was a decrease from the normal. He did not have to urinate at night. He had sick headaches at times, but not so many during the last few years. Three and one-half months before his death he first noticed oedema of legs and feet which brought him to the hospital. He denied venereal infection and the Wassermann test was negative. His weight had been steady at 150 pounds.

Clinical examination showed slight puffiness of the face, no enlargement of the heart (later slight enlargement), normal heart sounds except for a soft systolic murmur at the apex. The pulse rate was slow (60) and the pulse was irregular in force and rhythm. His temperature was within normal limits, slightly irregular. The blood pressure was 165-78, gradually going up to 250. Legs, feet and scrotum were markedly oedematous. Clinically the tonsils appeared to be normal on repeated examination. The amount of urine secreted varied between 500-1000 cc.; occasionally it would rise to 1300 and more. The urine contained much albumin, varying numbers of epithelial, hyaline and granular casts, many leucocytes and many red blood cells. The specific gravity was low constantly, never over 1015. The phenolsulphonephthalein secretion was fairly good (1 hr. 35%; 2 hr. 20%) but later dropped to 35% in two hours. In the beginning the haemoglobin content of the blood was 80% but it gradually dropped to 33% and the red blood cells decreased proportionately. A blood urea determination was made 2½ months before his death and 0.113 grams were found in 100 cc.

After some days in bed and with proper treatment the oedema disappeared almost entirely but it reappeared later. The end of August the patient began to complain of headache and shortness of breath. An electro-cardiogram made at about this time showed evidences of hypertrophy of the left ventricle, also sinus irregularly. On October 3rd the patient had three severe convulsions and several more later. Towards the end of October he complained of headache, nausea and pain in precordium. He became very restless, nervous and showed muscular twitchings but he remained conscious to the end. The backgrounds of his eyes which at first were normal, later showed some haemorrhages.

The autopsy revealed numerous pus pockets in the shrunken tonsils, marked general oedema, ascites, marked concentric hypertrophy of the left ventricle, slight fibrous thickening of the valves on the left side, moderate recent arteriosclerosis of the peripheral arteries, late subacute diffuse glomerulonephritis with moderate somewhat irregular inflammatory thickening of the connective tissue (kidneys about normal size, slightly granular), moderate fairly old arteriosclerosis of larger arteries of kidneys and more or less severe recent endarteritis in some of the arterioles, terminal hypostatic broncho-pneumonia.

Some of the sections from medium sized arteries show fairly recent lesions in the intima as follows: The endothelium is swollen and lifted off irregularly; the intimal cells are swollen and evidently proliferated; leucocytes, both polymorphonuclears and lymphocytes are present in small numbers; there are no lesions in media and adventitia. The intima of the aorta showed a moderate old fibrous thickening with a recent exacerbation in the superficial layers.

(5) (XX-125, L. H. 50233.) Man of 30, old abscess in left tonsil, late subacute glomerulonephritis with hypertension and concentric hypertrophy of heart, moderate general arteriosclerosis with severe involvement of arterioles in kidneys, retinitis albuminurica, uraemia.

A. U., 30 years, Italian laborer; entered January 22, 1917, died March 13, 1917.

Personal history: Patient had the ordinary infectious diseases of childhood. When very young he had had sore throat frequently. In 1915 he had a papular eruption on his back which lasted three days. The Wassermann reaction of the blood, however, was negative and there were no other signs of syphilis. Otherwise he had always been in excellent health until October, 1916, when he first noticed that he felt languid at times and noticed that his eyesight was gradually failing. In December of the same year he began to have severe frontal headaches of several days' duration. For some time he had had to get up once or twice at night to urinate. He came to the clinic on account of his failing eyesight. He had lost about 10 pounds of his usual weight.

Clinical examination showed an albuminuric retinitis, chronic tonsillitis, a blood pressure of 243-190, no definite enlargement of the heart, thickening of superficial arteries, regular pulse, varying irregularly between 70 and 100 per minute, temperature between 98 and 101° F., much albumin in urine, also many hyaline, granular, fatty, epithelial and occasional blood casts and some white and red blood corpuscles. The amount of urine secreted during 24 hours varied between 500 and 1500 cc.; the specific gravity between 1010 and 1021. The urine was found sterile on bacteriological examination. When he entered he secreted about 30% phenolsulphonephthalein in two hours. There were 51 mgms. of urea in 100 cc. of blood. The blood was normal. While in the hospital the patient suffered from intense headaches and severe nosebleeds. In spite of all efforts he grew steadily worse. His blood pressure constantly fluctuated about 200. Spinal puncture in March released clear fluid under high pressure. Following the lumbar puncture he had two convulsions. By March 8th the amount of urea in his blood had risen to 378 mgms. in 100 cc. He complained of pains and hyperesthesia in the left lumbar region. At times he was quite disturbed mentally, noisy and delirious, and in the end he became entirely irrational and developed signs of terminal broncho-pneumonia. He had had no oedema at any time.

The autopsy revealed swelling of optic discs and white spots and haemorrhages in retina, chronic tonsillitis with old abscess in left tonsil (containing many diplostreptococci), late subacute haemorrhagic glomerulonephritis, with little shrinkage, very severe obliterating endarteritis in arterioles of kidney, very marked concentric hypertrophy of left ventricle, fatty degeneration of heart muscle, marked arteriosclerosis of branches of renal arteries, moderate arteriosclerosis and marked dilatation of all arteries, terminal broncho-pneumonia, central necroses in liver, severe anaemia and haematogenous pigmentation of spleen.

Sections of a large artery show lateral thrombosis (thrombus developing from atheromatous ulcer). The inner layers of the intima in aorta and smaller arteries are very cellular, the cells are swollen and degenerated, in places there is a heavy infiltration with lymphocytes.

I believe that this new series of cases of nephritis substantiates in every way my previous conclusions in regard to this disease, as published in my monograph in 1916.* It is unnecessary, therefore, to enter here into a renewed extensive discussion of the problems connected with this part of the subject.

So far as the arterial lesions are concerned, the recent changes in the arteries of the last group invite most careful attention. In my previous article on nephritis I have described in detail the development of the lesions in the arterioles of the kidney consisting in an early subendothelial lateral thrombosis followed later by fibrosis as a result of organization. The same process seems to occur in the arterioles of the spleen and possibly at times in those of the myocardium. At that time I had no clue as to the way in which the endarteritis was brought about in the larger arteries in the kidneys and elsewhere, because in them I never observed any evidence of lateral thrombosis followed by organization.

My impression now is, especially on the basis of my findings in Case 4 of this series of subacute nephritis, that in the larger arteries also there is some primary damage of the endothelium followed by an entrance of plasma and with it of leucocytes into the intima without coagulation of the plasma. This is followed by a swelling and proliferation of the intimal cells which gradually build up new fibrous and eventually new elastic tissue. Hand in hand with these proliferative processes there occur the usual degenerative lesions which, to my mind, are primarily located in the intimal cells and not in the interstitial tissue, although according to the more recent investigations in regard to the structure of the connective tissue this may be a distinction without much of a difference, since these structures are so closely united that it hardly appears wise to attempt to segregate them very sharply.

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* Ophüls, W., "The Pathology of Nephritis," Stanford University Publications, 1916.

RELATION OF ARTERIOSCLEROSIS TO DISEASE OF THE CENTRAL NERVOUS SYSTEM

As these conditions are comparatively simple, it is unnecessary to make any extensive comments upon them. For the same reason I present the histories and anatomical findings as briefly as possible.

I. *Anaemic Softening*

As is well known, these areas of softening are the result of complete or almost complete obstruction of branches of the cerebral arteries by arteriosclerosis, usually followed by thrombosis. Their size varies according to the size of the territory provided by the obstructed artery. They are frequently multiple. The functional derangements which they produce depend on their location.

The following cases of this kind were observed in our series:

(1) (XIX-91.) Mrs. R., 82 years old. She was found in an unconscious condition a few days before her death. She had had no brain symptoms preceding this attack.

Autopsy revealed marked atheroma of the aorta, moderate general arteriosclerosis, few small scars in the kidneys, *a normal heart,* marked sclerosis of the cerebral arteries and an anaemic softening of about two-thirds of her left hemisphere. She also had a senile gangrene of one foot.

(2) (XIX-78.) J. K., 80 years old. Ten years before his death he developed a right-sided hemiplegia with motor aphasia. The motor aphasia seemed to be improving somewhat during the last year of his life. He died of broncho-pneumonia.

Autopsy revealed moderate atheroma of the aorta, marked general arteriosclerosis, few small scars in the kidneys, *normal heart,* marked arteriosclerosis of the cerebral arteries, softening of the left temporal lobe.

(3) (XIX-96.) S. W., 58 years old. Four years before his death his right side became paralyzed and he had trouble in speaking and in reading. His vision also seemed defective on the right side of both eyes. Clinical examination showed a right-sided hemiplegia, visual aphasia and alexia, right hemianopsia, arterial sclerosis and signs of "myocarditis." He died of broncho-pneumonia following carcinoma of the oesophagus.

Autopsy revealed marked atheroma of the aorta, marked general arteriosclerosis, many small scars in kidneys, *normal heart,* very marked arteriosclerosis of the cerebral arteries, large old area of softening in left temporal lobe extending into occipital lobe.

(4) (XIX-26.) F. B., 60 years old. Patient had had signs of an arteriosclerotic psychosis and a left-sided hemiplegia for many years. He died of broncho-pneumonia.

Autopsy revealed marked atheroma of aorta, moderate general arteriosclerosis, many small scars in left kidney, very marked arteriosclerosis of right renal artery with complete atrophy of right kidney, slight concentric hypertrophy of left ventricle, very marked arteriosclerosis of the cerebral arteries, many areas of cortical softening on both sides and area of softening in right thalamus opticus, broncho-pneumonia.

(5) (XXI-54.) Mrs. S. M., 72 years old. Patient had been generally in good health until one week before death, when she developed a paralysis of her right side with rather gradual onset and aphasia. She had had a similar attack with recovery five years before. Clinical examination during her last illness showed a blood pressure of 175–129 and the presence of some albumin and some casts in her urine. The Wassermann reaction of her blood was negative. She died of broncho-pneumonia.

Autopsy revealed slight atheroma of the aorta, moderate general arteriosclerosis, small scars in kidneys and in myocardium, very marked concentric hypertrophy of the left ventricle, very marked arteriosclerosis of cerebral arteries, partial occlusion of right middle cerebral artery by lateral thrombosis, large area of softening in basilar ganglia on left side involving nucleus caudatus, almost entire nucleus lentiformis, anterior and upper part of the thalamus opticus. She also had a healed endocarditis of the aortic and mitral valves, with stenosis of the mitral orifice, a marked hypertrophy of the right ventricle and a beginning cyanotic atrophy of the liver.

(6) (XIX-16.) M. McC., 60 years old. Patient had his first stroke with general prostration but without localizing symptoms ten years before death. It was then regarded as a sunstroke and he partly recovered from it. Two years later he had another stroke accompanied by paralysis. When he came to the hospital he complained of headache, inability to speak, lack of concentration, paralysis of left side including seventh and twelfth cranial nerves. He had a blood pressure of 244–200. He died of bulbar paralysis.

Autopsy revealed a marked atheroma of the aorta, a very marked general arteriosclerosis, very marked concentric hypertrophy of the left ventricle, marked sclerosis of cerebral arteries, large area of softening in region of right internal capsule involving nucleus caudatus, lentiformis and thalamus opticus, small old cyst in right side of pons.

(7) (XXI-14.) Mrs. B., 35 years old. Patient was mentally disturbed for about one and one-half months, was noisy and violent, had numerous general and partial convulsions, and died in coma.

Autopsy revealed marked atheroma of aorta, general arteriosclerosis of apparently recent development, large scars in kidneys, marked hypertrophy and dilatation of the heart, apparently normal cerebral arteries, recent areas of softening in left hemisphere of cerebellum, and another one in the anterior lateral part of the right occipital lobe. (For details see page 71.)

These are all simple, clean-cut cases of obstruction of various cerebral arteries. If general circulatory disturbances were present, they were compensated and did not directly participate in the causation of the death of the patient.

The frequency of lesions depending on the obstruction of the left middle cerebral artery resulting in right-sided hemiplegia and aphasia is quite striking.

Case 3 is of some interest, because in this patient the softening extended into the occipital lobe and caused hemianopsia.

Case 4 is a good example of the multiple cortical lesions usually encountered in cases of arteriosclerotic psychosis.

Case 5 was complicated by mitral stenosis, which, however, at death was still in a state of compensation.

In Case 6, no doubt the small old softening in the pons caused the attack of sudden prostration which was regarded as a sunstroke ten years before the death of the patient.

Cases 5, 6, and 7 prove that anaemic softening, although more common in cases without hypertension, does occur in patients with high blood pressure.

II. *Haemorrhagic Softening*

(1) (XX-139.) W. S., 50 years old. When 25 years old patient contracted syphilis, which was poorly treated. When he came to the hospital his blood yielded a ++ Wassermann reaction. Three and one-half months before death signs of heart disease developed; one day before death his entire left side, including face and tongue, suddenly became completely paralyzed; brought to the hospital, he became noisy and delirious and died in collapse. His blood pressure registered 160-110.

Autopsy revealed moderate atheroma of the aorta, marked general arteriosclerosis, few small scars in kidneys, marked hypertrophy and dilatation of the heart; severe, probably syphilitic, disease of the cerebral arteries; large cortical and subcortical area of haemorrhagic softening of the right hemisphere. (For details see page 59.)

(2) (XX-112.) H. D. C., 62 years old. Patient had had signs of heart disease for two years. His blood showed a positive Wassermann reaction and while at the hospital he exhibited a papulo-vesicular skin eruption. He had a blood pressure of 130–95. One week before he died

he suddenly developed a right-sided hemiplegia and aphasia without loss of consciousness. He died of broncho-pneumonia.

Autopsy revealed slight atheroma of the aorta, moderate general arteriosclerosis, few small scars in kidneys, moderate hypertrophy and dilatation of both sides of heart, moderate sclerosis of cerebral arteries, diffuse haemorrhagic infiltration of left nucleus caudatus, nucleus lentiformis and anterior part of thalamus opticus. (For details see page 60.)

It is usually stated that the occurrence of red softening of the brain after arterial occlusion depends on whether blood is carried into the area of softening and oozes from the blood vessels into the softened tissues. Judging by our knowledge in regard to the occurrence of haemorrhagic infarcts in other organs, it is assumed that in case of haemorrhagic softening the blood is provided either by a small anastomotic arterial branch or by regurgitation from congested veins in the neighborhood. It appears to me, however, that before accepting this idea the cases of haemorrhagic softening of the brain should be more carefully investigated than they apparently have been so far, and that for the present it is better to acknowledge that the exact conditions under which this form of softening develops are not clearly understood. It certainly would be of some interest to know whether high blood pressure favors this development.

It is probably a mere matter of chance that both of our patients happened to be syphilitics.

III. *Haemorrhage*

(1) (XIX-67.) Mrs. A. McC., 32 years old. Patient had apparently been well until seven months before death, when she lost control of her right leg, then of her right hand, and then lost consciousness. When she came to the hospital she had a right-sided flaccid hemiplegia and motor aphasia, and signs of nephritis were discovered. Her blood pressure was 220–65. She died in uraemia.

Autopsy revealed slight atheroma of the aorta, little general arteriosclerosis, severe chronic nephritis, marked hypertrophy and dilatation of the heart, normal arteries at base of brain, old haemorrhagic cyst about 5 cm. in diameter in posterior part of left frontal and anterior part of left temporal lobes near Sylvian fissure. (For details see page 80.)

(2) (XX-32.) L. B., 42 years old. Signs of severe nephritis made their appearance four and one-half months before death of patient. He died in an apoplectic seizure with paralysis of the left side, including face, and spasms in his right arm and leg. His systolic blood pressure was over 200.

Autopsy revealed moderate atheroma of aorta, marked general arteriosclerosis, severe chronic nephritis, hypertrophy and dilatation of the heart, marked arteriosclerosis of cerebral arteries, large haemorrhage in right hemisphere underneath motor cortex with perforation into lateral ventricle. (For details see page 77.)

(3) (XXI-6.) Mrs. L. B., 44 years old. Patient had shown signs of nephritis for 15 years. She died in the apoplectic attack showing a right-sided hemiplegia. Her systolic blood pressure was 240.

Autopsy revealed marked atheroma of the aorta, marked general arteriosclerosis, large scars in kidneys, concentric hypertrophy of left ventricle, very marked sclerosis of cerebral arteries, recent haemorrhages in region of left internal capsule and in right hemisphere of cerebellum. (For details see page 72.)

(4) (XIX-77.) C. S., 57 years old. Few days before his death patient had a stroke with flaccid left-sided hemiplegia. He never recovered consciousness. No history was obtained.

Autopsy revealed very marked atheroma of aorta, very marked general arteriosclerosis, many large scars in kidneys, slight hypertrophy of left ventricle, marked sclerosis of cerebral arteries, haemorrhage into brain. (The brain was not opened at autopsy to permit later study for exact localization.)

(5) (XIX-36.) Mr. G., 60 years old. Three days before death patient had a sudden stroke with unconsciousness and spastic hemiplegia on right side. He had had symptoms of "kidney disease" previously. He died while still unconscious, from broncho-pneumonia. His maximal systolic pressure was 200.

Autopsy revealed moderate atheroma of aorta, marked general arteriosclerosis, large scar in one kidney, very marked concentric hypertrophy of left ventricle, *large arteries of brain only slightly diseased,* large haemorrhage in nucleus caudatus and thalamus opticus on right side with perforation into lateral ventricle, *syphiloma of liver.*

(6) (XX-183.) S. B., 82 years old. Patient had an apoplectic attack two days before death. He remained unconscious and showed spastic paralysis of right arm and of left side. No history was obtained. His blood pressure was 170–90.

Autopsy revealed *syphilitic aortitis,* marked general arteriosclerosis, moderate concentric hypertrophy of left ventricle, very marked sclerosis of cerebral arteries, recent subventricular haemorrhage into left basilar ganglia with perforation into left ventricle and partial filling of right ventricle.

These cases are arranged according to the age of the patient.

They bring out clearly the important relation of chronic nephritis to early cerebral haemorrhage.

The arteries generally and those of the brain were practically normal in the first patient, a woman 32 years of age. This, of course, does not prove that the artery which actually burst was not badly diseased. Still, I consider this rather unlikely. In all other cases there was a well-developed sclerosis of the cerebral arteries, with one more exception in Case 5.

Cases 5 and 6 were the only ones in which there was any clinical or anatomical evidence of syphilis.

The systolic blood pressure was uniformly high in all cases, showing the great importance of this factor in the production of the haemorrhages. There may be one possible exception in Case 4, in which the blood pressure had not been measured and where the left ventricle was only slightly hypertrophied.

The tendency for a localization of these haemorrhages in the basilar ganglia is also clearly shown. They are usually single, but they may be multiple and simultaneous.

Their frequently fatal character is also strongly emphasized by our records.

GASTRO-INTESTINAL LESIONS

In an article of mine on the relation of gastric and duodenal ulcer to vascular lesions* I have restated the reasons why it seems highly probable that these ulcers are caused by local disease of the arteries which may or may not be associated with general arteriosclerosis. In individuals under 30 they are usually due to a peculiar local endarteritis, but in the much more common ulcers in individuals over 30 years the lesions in the blood vessels resemble those of ordinary arteriosclerosis. The following cases of gastro-duodenal ulcers occurring in our series have been arranged according to the age of the patients.

(1)* (XXI-168.) Th. K., 35 years old. Patient had had no previous symptoms. Acute peritonitis from perforation developed 14 days before death.

Autopsy revealed slight atheroma of aorta, moderate arteriosclerosis of coronary arteries, slight arteriosclerosis of small arteries of kidneys, perforated acute duodenal ulcer.

(2) (XX-185.) J. C., 41 years old. For the last two years patient had pains in stomach, one to two hours after meals. During the last two weeks he vomited everything he ate. He had never before had bleeding, but he was now evidently losing blood rapidly and his haemoglobin was reduced to 25 per cent. At an exploratory laparotomy the ulcer was not found.

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* Ophüls, W., "The relation of Gastric and Duodenal Ulcer to Vascular Lesions," *Arch. of Int. Med.* **2**, 469, 1913.

Autopsy revealed slight atheroma of aorta, moderate sclerosis of the arteries in the spleen and more marked disease of those in the kidneys. The larger arteries were normal. In the duodenum just below the pylorus there was found a chronic ulcer nearly 5 cm. in diameter over the pancreatico-duodenal artery with erosion of one of its branches. The intestines were full of blood.

(3) (XIX-147.) F. C., 45 years old. Patient had the usual symptoms of a chronic ulcer and a successful gastro-enterostomy had been performed three days before death. He died of broncho-pneumonia.

Autopsy revealed syphilis of the aorta, moderate arteriosclerosis of small arteries in spleen and kidneys, normal large arteries, large transverse chronic ulcer of duodenum adherent to pancreas.

(4) (XX-93.) G. K., 47 years old. Patient had the first symptoms of gastric ulcer at age of 25, first haemorrhage at 37 and again at 43. He came to the hospital complaining of vomiting blood and of passing blood with stools. The ulcer was resected. One month later he died of pulmonary tuberculosis.

Autopsy revealed slight atheroma of aorta, moderate arteriosclerosis of the renal arteries (more marked in the smaller branches), large scars in kidneys. In duodenum near pylorus, over pancreas, there had been a large crater-shaped chronic ulcer. Microscopic sections showed marked sclerosis of arteries at base of ulcer.

(5) (XIX-152.) J. J., 51 years old. Patient never had any symptoms of ulcer. He died of decompensation of the heart.

Autopsy revealed marked atheroma of aorta, marked general arteriosclerosis, hypertrophy and dilatation of heart, punched-out oval ulcer about ½ cm. in diameter in posterior wall of *fundus* of stomach.

(6) (XXI-114.) Mrs. E. T., 54 years old. Patient complained of loss of appetite six months before death. For the last three months she had had sharp pains in stomach after eating. This would be followed by vomiting. In the end the pain was almost continuous. Death from chronic tuberculosis of lungs and intestines.

Autopsy revealed moderate atheroma of aorta, slight arteriosclerosis of renal arteries (very marked sclerosis of smaller branches), large scars in kidneys, nearly healed chronic ulcer of stomach.

(7) (XXI-135.) Mr. M., 55 years old. Patient had indigestion for past year, no pain in stomach. Acute perforation occurred four days before death.

Autopsy revealed moderate atheroma of aorta, moderate general arteriosclerosis, marked sclerosis of arteries in spleen and kidneys, slight hypertrophy of left ventricle, perforated chronic duodenal ulcer about 3½ cm. in diameter just outside the pylorus.

(8) (XIX-113.) Mr. D., 60 years old. Patient had had the usual symptoms of a chronic ulcer. Gastro-enterostomy had been performed successfully, but patient died of lobar pneumonia.

Autopsy revealed slight atheroma of aorta, slight arteriosclerosis of coronary arteries, normal arteries otherwise, chronic ulcer about ½ cm. in diameter in duodenum ½ cm. away from pylorus.

(9) (XXI-58.) H. W., 62 years old. Patient had had gastric pains three hours after meals for seven or eight years. Two weeks before death perforation occurred, followed by acute peritonitis.

Autopsy revealed slight atheroma of aorta, marked sclerosis of small arteries in spleen and kidneys, normal arteries otherwise, perforated chronic ulcer of duodenum, about 1½ cm. in diameter, just outside of pylorus.

(10) (XX-192.) H. C., 64 years old. Patient had been suffering from epigastric pain and vomiting. The diagnosis of duodenal ulcer had been made one and one-half years before death. He died of carcinoma of bile duct.

Autopsy revealed slight atheroma of aorta, moderate sclerosis of arteries in spleen and kidneys, normal arteries otherwise, chronic duodenal ulcer about 2 cm. in diameter, 2 cm. from pylorus, with constriction. Microscopic sections of ulcer showed marked endarteritis in arteries at base of ulcer.

(11) (XIX-27.) P. S., 75 years old. Patient never had had any ulcer symptoms. He died of decompensation.

Autopsy revealed marked atheroma of aorta, very marked general arteriosclerosis, hypertrophy and dilatation of the heart, chronic transverse, fairly shallow ulcer in first third of duodenum. (For details see page 63.)

(12) (XX-104.) J. R., 80 years old. Patient never had any ulcer symptoms. He died in coma, having developed broncho-pneumonia.

Autopsy revealed very marked atheroma of aorta, marked general arteriosclerosis, many old scars in kidneys, hypertrophy of heart, old deep ulcer about 1 cm. in diameter in pyloric region of stomach. Microscopic sections showed marked arteriosclerosis of arteries at base of ulcer. (For details see page 65.)

This complete series of our cases of gastro-duodenal ulcer during this period shows again clearly the close relation of general arteriosclerosis in some and of local endarteritis in others to the development of these ulcers. That in older people even the vascular lesions may be fairly well limited to the stomach and duodenum is shown in Cases 8, 9, and 10. In Cases 11 and 12 the ulcers were discovered unexpectedly at autopsy in patients with severe general arteriosclerosis, hypertension and decompensation.

Whenever the ulcers were examined microscopically, which unfortunately was done in a few cases only, severe arterial lesions were found in the blood vessels at the base of the ulcer.

The prevalence of duodenal ulcer over gastric ulcer is unusually strikingly shown in this series, there being nine duodenal and three gastric ulcers. Of the gastric ulcers, one was situated in the fundus. The disturbances produced by these ulcers in the characteristic cases were those usually described, as pain in the region of the stomach after eating, vomiting, haemorrhage, and perforation.

CONCLUSIONS

1. The development of arteriosclerosis is closely connected with injury to the arteries resulting from various infections.

2. Chronic septic infections of the rheumatic type seem to play the most important role in this connection.

3. The arterial lesions seem to reach their full development after the active infectious process has long subsided.

4. In our series there is no striking difference in the relative incidence of the disease in males and females. (This remains to be confirmed by study of a larger material.)

5. The close etiological relationship explains the frequent association of arteriosclerosis and nephritis. In some cases the causative agent or agents affect principally the blood vessels, in others principally the kidneys, and there are border-line cases where the damage is fairly equally distributed between the two systems. It is misleading and confusing to look upon the renal lesions as a result of the changes in the arteries or vice versa.

6. Syphilis is of great importance in the production of disease of the aorta and of the cerebral arteries. Its etiological importance in arterial disease elsewhere in the body is still undetermined but does not appear to be very pronounced.

7. The tissue changes in arteriosclerosis are partly inflammatory but to a great extent degenerative and reparatory. In the arterioles the initial lesion seems to be a lateral subendothelial hyaline thrombosis followed by organization; in the larger arteries we find evidence of endothelial damage permitting the entrance into the intima of blood plasma and blood cells, followed by proliferation and degeneration.

8. General arteriosclerosis is sometimes, but by no means always, associated with hypertension.

9. The degree of hypertension which develops in purely arterial cases is not usually very high* and is apt to be considerably reduced

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* Further clinical observations in early cases of this character will be necessary to make sure of this point.

(sometimes to normal or below) during and between periods of decompensation.

10. The highest degrees of hypertension develop in nephritis or in arteriosclerosis associated with nephritis.

11. Hypertension is largely a functional condition, probably due to an increased tonicity in the small arteries and arterioles.

12. Myocardial lesions may develop as the immediate result of arteriosclerotic obstruction in the coronary arteries, as a result of myocarditis and as a result of a combination of the two.

13. The functional importance of the more localized myocardial lesions has not been finally determined.

14. The comparatively limited focal lesions in the kidneys which are so frequently associated with arteriosclerosis are of no functional importance. (I believe it is misleading to speak of them as arteriosclerotic scars, because this produces the impression that the arteriosclerosis is the all-important factor in their production, whereas most of them no doubt are remnants of focal nephritis due to the action of the same cause both on the renal arteries and on the renal tissue.)

15. Focal lesions in the kidneys which extend beyond certain limits may influence the clinical picture quite seriously.

16. The functional disturbances in the cases with diffuse involvement of the kidneys are quite characteristic, but in each case the intensity of the various disturbances may vary very considerably and quite independently of each other because they are merely associated phenomena, not directly dependent upon the local processes in the kidneys, with the exception, of course, of some of the changes in the urine.

17. The lesions produced in the brain by arteriosclerosis are of a purely mechanical nature.

18. Chronic ulcers of stomach and duodenum are the result of local arterial disease which frequently is part of a general arteriosclerosis.

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